THE PHYSIOLOGIST

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Health Benefits of Animal Research

The Cat as a Research Subject

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Cats made the cover of *Time* magazine, December 7, 1981 (135). They made it for their capacity as people pleasers, their role as the country's most adaptable companion animal, and their potential as a new source of revenue for cartoonists and merchants who have recognized the cat's national popularity. It is estimated that there are 34 million cats inhabiting 24% of the households in America and another 15 million who are homeless. In the past 30 years the health of the house-dwelling cat has been improved to such a degree that a life expectancy increase of 6–8 years allows many felines to reach the 16–20 years age range. Improvement in the feline's health has been brought about, in great part, by better nutrition; new and improved diagnostic procedures, surgical techniques, and treatment and drug therapies for such conditions as feline urolithiasis, skin disorders, fractures, conjunctivitis, anemia, tumors, and pneumonia; and vaccines for the prevention of many life-threatening diseases such as feline enteritis, rhinotracheitis, pneumonitis, and most recently for feline leukemia (92, 101, 102, 118, 121). This improved quality of life for felines could not have been brought about without the aid of biomedical research – research which often relied on the cat as the subject.

Not dealt with in the *Time* article was the cat's contribution to medical research, perhaps because it is a very unpopular subject with a small segment of the public. However, cats, as well as dogs, rabbits, horses, nonhuman primates, pigs, and other species, have long been recorded as contributors to our vast store of medical knowledge. This article is intended to review the role the cat has played in biomedical research, the many diseases the cat suffers that have human counterparts (20, 37, 106), and the benefits that both humans and domestic cats have received as a result of medical research advances.

Animals in Research

Throughout history biomedical research has involved both humans and animals; the interrelationship of the disease processes between the two has long been recognized, and the use of animals to study anatomy, physiology, disease and behavior has been well recorded. Animals were a favorite subject of the early cavemen as evidenced by the many drawings on their cave walls, drawings depicting not only appearance but also behavior. As far back as 1500–500 B.C. there are indications in early Vedic (Hindu) records of animals being observed by man for scientific purposes. In 300 B.C., in Alexandria, Egypt, Erasistratis placed live birds in closed containers and withheld food to observe the consequences of losing body humors. This is believed to be the first recorded attempt to use live animals for research. The philosopher Aristotle (384–322 B.C.), also a biologist and the son of a physician, founded the sciences of physiology, zoology, and comparative anatomy as a result of his observations of animals. Galen (130–200 A.D.), a physician, anatomist, physiologist, and philosopher, was the founder of experimental physiology. His animal studies were designed to be applicable to humans; their accuracy and completeness improved markedly the understanding of the human body. After the fall of the Roman Empire and during the Dark Ages, the decline that occurred in the arts and sciences was quite evident in both human and veterinary medicine. The unity that had existed between the two branches of medicine did not reappear until the Renaissance. The seventeenth and eighteenth centuries saw significant medical advances, many the result of animal studies. (22, 41, 78, 91, 146)

Medical research has always depended heavily on animals as subjects. Often, these have been normal healthy animals in which the disease or abnormality to be studied could be introduced experimentally. Frequently, however, they have been animals in which there has occurred a spontaneous disease or abnormality which mimics a human condition. More such animal model disease systems are essential to study the mechanisms underlying the broad spectrum of human health problems. No single species can provide all of the answers. Bustad et al. (19) point out that the species chosen must be evaluated on its distinctiveness (a distinguishing characteristic that mimics a particular property in the human disease entity); fidelity (overall faithfulness to the human condition); and reproducibility (ability to produce sufficient numbers of animals to study the disease adequately). Without these considerations, the most carefully designed experiment may lack integrity.

History of Cats in Research

Because of the similarity in the cat's general function of cells, blood, and other tissues to that of man, cats have been, are, or may be excellent animals models for many human diseases or conditions. According to British scientist, Patricia Scott (141), the use of cats for biomedical research can be dated back to the publication of a textbook in 1881 by St. George Mivart (107), a British zoologist. More than 300 pages are devoted to a detailed and accurate anatomical description of the cat.

In 1894, Marey, a French physiologist, used the motion-picture camera to illustrate how the cat's body changed position when it was dropped from a height, landing eventually on its feet. This observation led other

physiologists in the early 1900's to examine the physiology of the falling reflex and to come to the conclusion that the brain and either the eyes or the balancing mechanism ("vestibular organs") in the ears were essential to accomplish the feat. It was not determined, until 1960, that, of the two systems, the eyes were the more important. (14, 104)

In 1897, only two years after the discovery of X-rays by Roentgen, Walter B. Cannon, a Harvard physiologist, used the cat to achieve the first visualization of the gastrointestinal tract (21). Not only was he able to observe the normal functioning gastric system, but he also observed that peristalsis stopped whenever his feline subjects became anxious or frightened. Reassurance and petting restored normal functioning. These experiments were the beginning of Cannon's well-known research on the physiology of emotion.

In 1898, Edward L. Thorndike, a psychologist, constructed his famous puzzle boxes in which cats, to obtain food, learned to perform certain tricks such as pulling cords, pressing levers, and stepping on platforms. Cats became common subjects for laboratory tests of learning ability, the results of which have been applied to human educational practices. Evidence that the normal development of visually guided reaching behavior results from self-produced movement and the feedback associated with it has been shown through deprivation studies in cats; it has also been shown that postnatal development of the brain is directed by early sensory experience. In addition, deprivation studies in cats, as well as in other species, have reinforced the observations made on poorly mothered human infants (14).

In the area of brain research, the cat has been used extensively. According to Boudreau and Tsuchitani (18), "More is known about the anatomy of the cat sensory systems – e.g., the skin, joint, muscle, and auditory senses – than those of any other animal. . . . Most of the neurophysiological work in audition, skin, muscle, joint, and some chemical senses has been performed in cats. No other animal has been studied in such detailed fashion." The uniformity of the cat's head makes it the experimental animal of choice – i.e., "an atlas of one cat brain is an atlas of all cat brains" (14).

Mitruka and colleagues, in their book, *Animals for Medical Research* (106), list a number of reasons for using cats in biomedical research, such as ease of obtaining and maintaining; convenience of size and anatomy, especially for studies involving physiology and the nervous system; susceptibility to certain viral infections of the nervous system and brain comparable to conditions in humans; occurrence of blood cancers and solid tumors such as lymphomas, leukemia, and adenocarcinoma and endocrine tumors comparable to those of humans; and little evidence of the inherent variability seen in rabbits and dogs. The cardiovascular, digestive, and neuromuscular systems of the cat are very similar to those of the human. In addition, they note that cats have contributed to important discoveries regarding reflex action, synaptic transmission, perception of light and sound, and secretion of digestive glands; behavior of cardiovascular, respiratory, excretory, and synthetic drugs; and effects of drugs on the nervous system.

The *Bibliography of the Cat; Revised Edition* (16), January 1976, edited by Berman and Liddle, "originated as an aid in the definition of the domestic feline as a laboratory animal." Drawing from a collection containing an estimated 7,000 references citing cats in biomedical research, this revision contains more than 2,300 references which range from the late nineteenth century to 1975. It is divided into three parts: *1*) author listing, *2*) article listing, and *3*) cross-reference listing. There is also a list of 125 subject descriptors which have been cross-indexed. The number of titles involved for each subject descriptor is listed. There are 10 areas with more than 100 titles. These are brain 107, genetics 197, head-eyes-ears 112, neurophysiology 190, nutrition 134, parasitology 135, pharmacology 179, surgery and techniques 180, tumors and neoplasms 253, and virology 166.

MEDLARS II, the National Library of Medicine's Medical Literature Analysis and Retrieval System, has in its data bank approximately 8,800 bibliographic citations linking the cat to studies in almost all areas of biomedical research.

Research Areas-Systems in Which the Cat Has Been Used or Has Potential for Use

At one time or another, the cat has contributed to studies of human anatomy, physiology, illness, and behavior. Presented in this paper, by major research areas or systems, are many of the diseases and conditions for which the cat has been used, or has potential for use, and the human counterparts of those diseases and conditions.

The cat, as discussed earlier, has been showing the way to new medical knowledge for many years. Cats were first used in socialization studies and then learning studies. As neuroscientists developed reliable anesthetic methods and delicate instruments to examine the nervous system, cats were used to examine a variety of neurological problems, such as epilepsy, deafness, vision problems, tremors, and ataxia, common to both cats and people. As more and more information was accumulated by veterinary scientists about the infectious and metabolic diseases of cats, it became evident that man and the cat had many diseases and conditions in common. Although most of the diseases are not directly transmissible from cat to man and vice versa, the two species resemble each other closely enough that the research findings in one species are applicable to the other species. Some of the more familiar human diseases that have been studied in the cat are diabetes, glomerulonephritis, breast cancer, leukemia, lupus, aortic thrombosis, and hemophilia.

Aging

As in man, degenerative diseases occur in all species of animals as they grow older. The National Institute on Aging (NIA), NIH, sponsored a workshop in December 1976 to review the use of various vertebrate species as animal models for research on aging. As a result of this workshop, a report was published in 1981 entitled *Mammalian Models for Research on Aging* (98). The section prepared by the Subcommittee on Carnivores contains a great deal of information citing the use, and potential for future use, of the cat as a model for research on aging.

As pointed out in the report, survival data for cats maintained under defined conditions is meager. There have, however, been reports on the causes of death in pet cats over 10 years old and on the pathological findings in aged pet cats from animal hospital populations. These show that neoplasms, excluding leukemias, increase significantly with age; trauma is a frequent cause of death or disease in cats from 4 to 9 years of age; an age-related increase in medial hypertrophy of the pulmonary arteries occurs; and in males urolithiasis is a common cause of death.

The cat has a relatively long life span. Although it is difficult to obtain information over the life span of one animal, it is possible to observe the accumulated subtle effects due to aging and deleterious influences. The long life span combined with the genetic heterogeneity of most breeds permits a number of natural diseases to occur and to be studied without being overshadowed by a single disease entity. Cats share the stage with dogs and monkeys as being the species most frequently studied as "old" animals.

Mention is also made, both in the NIA report (98) and by Bustad et al. (19) of the companion animal population, in which large numbers of cats are kept by modern society until they are aged. As noted previously, it is not uncommon for well-cared-for cats to reach the age range of 16–20 years. It is of interest that many of the procedures used to study aging processes do not require surgical intervention nor do they adversely affect the health and well-being of the animal, thus making pet populations ideal for cross-sectional studies of animals of different ages as well as longitudinal studies of the same animals. Studies of this type with pets will yield information of relevance to both man and pets—an important factor in view of the increased interest in the role of companion animals, especially for the older population.

Cats are playing a very significant role in the human-animal bond, a subject of interest for many years and the topic of numerous meetings in the United States, Canada, and several European countries. The existence of the human-animal bond can be traced back some 30,000 years and the prescribing of animals for treatment, hundreds of years. Although animals (cats, dogs, birds, fish, rabbits) are being used for their therapeutic value with the mentally retarded, physically handicapped, and prisoners, one of their most valuable contributions is with the aging population, especially with those persons who are living alone or are confined to nursing homes; cats are the animal most often used in these settings.

The aging process in man effects changes in all of the body systems and may lead to chronic and/or degenerative type illnesses which are not solely diseases of aging. These will be discussed under the heading of the system in which they occur.

Alimentary-Gastrointestinal System

The cat has a number of features in common with man, making it a useful model for the study of gastrointestinal disease syndromes. As previously noted, Cannon in 1897 studied the function of the feline gastrointestinal tract using X-rays.

Esophageal Achalasia

Esophageal achalasia or cardiospasm in man is a neuromotor disorder in which the lower esophageal region fails to dilate in response to an oncoming wave of peristalsis. Food is therefore blocked from passing into the stomach, leading to vomiting and possible serious disability. In humans, abnormal parasympathetic innervation of the myenteric plexus is blamed for cardiospasm. A similar hereditary condition, called megaesophagus, is found in the cat. It appears to share several of the characteristics of the condition found in children. (32, 43, 98)

Cancer-Neoplasms

As discussed in the NIA report (98), oral and pharyngeal neoplasms are commonly seen in the cat and bear some similarity to the disease in man; salivary gland neoplasms, although rare in the cat, may provide a good model for study; salivary gland tumors rarely occur; gastrointestinal neoplasms, which occur in the cat and bear some resemblance to the comparable lesion in man, may be reasonable models for the study of factors of importance in the human disease; gastric carcinomas are rare in the cat; and small intestinal adenocarcinomas and lymphomas are reported to occur with the same incidence in both the cat and man. Lymphomas in the cat have been well studied and appear to be good models of the human counterpart.

Auditory

The cat shares with man and the higher nonhuman primates a very well-developed hearing and balance system. The cat can be trained to respond to many behavior cues which can be given through auditory stimuli; therefore, it is an excellent animal in which to study hearing defects. The cat has some hearing defects that occur normally.

Deafness

In white cats, there is frequently a bilateral or unilateral hereditary degeneration of hearing. Deafness in this animal was discovered at the turn of the century; this deafness, caused by degeneration of the eighth cranial nerve, has been well studied in the cat. Deafness in the white cat and Waardenburg syndrome in the human have a number of features in common. In both cases there is hypopigmentation or white spotting, sensorial neural deafness, and cochlear degeneration. The white-color coat is an inherited autosomal dominant trait, but apparently more than one locus is involved. The expression of eye color and deafness appear to be independent of each other. (50, 66, 97)

Auditory Trauma

The cat, as well as the human, is susceptible to high-volume sound trauma to the ear. This susceptibility has made the cat very useful in the study of loss of hearing in people due to high-volume noise from construction work, heavy manufacturing assembly, or operation of noisy equipment. While preventive measures can be taken in these instances to avoid injury, often the use of hearing protectors increases hazards because audible warnings are not perceived until it is too late. Studies in the cat have given us some idea of the level of noise that can be expected to be damaging over a certain period of

time as well as some information on the pathology of this damage (66).

Tinnitus

Tinnitus is a constant internally generated noise, generally at a high pitch, which is often heard in the human ear and may be the result of earlier acoustical exposure to high levels of noise. Studies in the cat have indicated that the signal causing the noise in the ear is cochlear in nature and may relate to changes in middle ear pressure. It is now known that in the cat, as in man, the noise from tinnitus can be suppressed by tones of high frequency, but this is not a satisfactory solution to the problem, since what is desirable is to eliminate totally the tone produced by the tinnitus. Hopefully, continued studies in the cat and man will provide, in time, some insight into the prevention and therapy of this unpleasant condition. (49)

Behavioral Research

Human behavior can be studied comparatively in animals. Mitruka et al. indicate that this is most successful when the process being studied is fairly well defined and when there is a limited specific objective in mind. Behavioral scientists use the cat for studies of behavioral development, comparative evaluation, and behavioral assessment. Earlier behavioral studies with the cat were most likely a result of the "evolutionary fervor created by Darwin's writings together with the orientation of psychology of that day toward broad theories and overall systematization" (106). More recently, cat experimentation has been directed toward " the neuroanatomical and neurophysiological researches which are given behavioral meaning" and "some physiological or biochemical variable which may be related to certain behavioral sequelae" (106).

Examples of human conditions studied in the cat include neuroses, amphetamine psychosis, adaptive behavior, learning and memory processes, depressive disorders, observational learning, socialization, imitation solution of oddity problems, and habit formation. It is expected that the cat will continue to be an animal of choice for many of these behavioral studies.

Cancer

Many animal species are subject to both spontaneous and induced malignant neoplasms (cancers), the second leading cause of death in humans in the United States (25, 112), and therefore provide excellent models in which to study the etiology, development, and treatment of human cancers. In addition to cancers of the gastrointestinal system noted previously, the cat has been used in studies involving lymphosarcoma, adenocarcinoma, malignant lymphoma, multiple myeloma, squamous cell carcinoma, acute lymphoblastic leukemia, aplastic anemia, mammary cancer, and pseudohyperparathyroidism and hypercalcemia of malignancy. The literature abounds with articles describing cancer research involving the cat.

Myeloproliferative Diseases

Both humans and cats fall victim to myeloproliferative diseases. Whereas the morphological origin of the neoplastic cell is usually identifiable, this is often not the case in the cat. These diseases are progressive in both species with death occurring in a relatively short period (98). Myeloma is a neoplastic proliferation of plasma cells that is occasionally observed in the cat and has been evaluated for its usefulness as a model of human myeloma (106).

Feline Leukemia-Sarcoma Viruses (Lymphoproliferative Diseases)

Of the many diseases cats and humans share probably one of the best known is leukemia. Acute lymphocytic leukemia, the most common form of cancer in children, accounts for 3,000 cases/year and is even more common in adults. Acute myelocytic leukemia is less frequent in children; the chronic form is found almost exclusively in adults. Leukemia morbidity figures in the United States total 19,000/year, with mortality about 14,000/year (103).

Barlough has written an excellent review of the feline leukemia virus (FeLV), a virus which he states is "responsible for the most important fatal infectious disease complex of American domestic cats today" (12). The causative agent of leukemia in the cat is a ribonucleic acid (RNA) virus belonging to the family Retroviridae. Not all retroviruses are oncogenic; those which are referred to as the RNA tumor viruses or oncornaviruses. Retroviruses have also been implicated in malignancies in several animal species other than the cat, among these are nonhuman primates and humans. Of great interest and importance currently are the reports of retroviruses associated with Simian Acquired Immune Deficiency Syndrome (SAIDS) (40, 72, 100) and with Acquired Immune Deficiency Syndrome (AIDS) of humans (13, 48, 56, 57, 69, 127, 138, 140).

Three members of the Retroviridae family are included in Barlough's discussion of the feline leukemia-sarcoma complex: FeLV, feline sarcoma virus (FeSV), and RD-114. Of the three, FeLV appears to be of the greatest clinical significance, in that it directly causes lymphoid malignancies, myeloproliferative disorders, several types of anemia, panleukopenia-like and thymic atrophy syndromes, at least one form of kidney disease, reproductive disorders, and a number of miscellaneous conditions. The most common neoplasm caused by FeLV is lymphosarcoma and accounts for about one-third of all feline neoplasms. Many other disease syndromes, indirectly related to FeLV infection, can also occur in the cat; these usually result from the immunosuppressive effects of the virus and may not show up for months or years. They include severe bacterial infections, infectious anemia, toxoplasmosis, oral infections, skin infections, respiratory infections and pneumonia, acute colitis, severe ear infections, haemobartonellosis, and infectious peritonitis. (12, 36, 38, 46, 47, 74, 75, 81, 118, 120, 122–124, 147, 148, 150)

Diseases associated with FeSV, in comparison to the number associated with FeLV, are of relatively minor clinical significance and include fibrosarcomas and malignant melanomas (1, 2, 12, 59, 60, 113, 145). The RD-114 retrovirus, the proviruses of which are present within the chromosomal DNA of all cells of all domestic cats, does not appear to be related to FeLV and FeSV; the association of RD-114 with the disease process and immunosuppression is under investigation (12, 62, 114–116, 123, 147).

Several tests have been developed which determine the FeLV or FeLV-immune status of the cat by detection of antigen or antibodies (12). These tests are aiding veteri-

narians in the control of feline leukemia. Work with the feline virus in comparative studies of human leukemia is aimed presently at detecting markers on cells indicating the presence of a leukemia agent in these cells.

There is no effective treatment known that will alter the course of FeLV-associated infections. For lymphoid malignancies, chemotherapy, surgery, and radiation therapy may be used to provide relief and to prolong life depending on the nature of the individual case. Myeloproliferative disorders may require whole-blood transfusions in addition to chemotherapy, but the results of such treatment have been disappointing. Nonregenerative anemia, one of the most common manifestations of FeLV, has been treated with whole-blood transfusions, and some researchers are testing the effects of interferon on the disease. Interferon is a substance that has recently come under consideration for its possible anticancer properties. FeLV provides an excellent model for this testing, the results of which may aid not only in the treating feline leukemia but also in providing valuable information in regard to the treatment of human cancers. (12, 149)

Research efforts aimed at finding an effective vaccine for feline leukemia continue. One vaccine has been patented and is awaiting government licensing (92, 101, 102, 119, 121). If successful, the techniques may prove useful to investigators in producing vaccines for the prevention of human retrovirus infections.

The feline retroviruses have been studied extensively in relation to their human counterparts (58, 61, 132, 137, 139). While there is no evidence that the cat virus causes leukemia in humans, the ability to study so similar a disease in a related species is very useful to cancer researchers. Viral agents as a possible cause of cancer in humans have not been ruled out. It is hopeful that research on this animal model will contribute to a fuller understanding of the role of this group of viruses in malignancy and cancer-related immunosuppression in all species. (36, 120, 123)

Pseudohyperparathyroidism and Hypercalcemia of Malignancy

Yarrington and Capen (158) have used cats to study comparatively the human condition known as pseudohyperparathyroidism (PHP) and hypercalcemia of malignancy. This involves the development of hypercalcemia associated with a malignant tumor, derived from nonendocrine tissue, which has not metastasized to bone and includes mammary cancer, malignant lymphoma, leukemia, and bronchiogenic carcinoma. In the cat, PHP is associated with lymphosarcoma involving the mediastinum, liver, jejunum, duodenum, and myocardium. Studies in the cat involve the investigation of the mechanisms of ectopic parathyroid hormone production by some nonendocrine tumors and the response to new chemotherapies.

Mammary Tumors

Mammary tumors are common in the cat and frequently spread. They are the third most frequent group of cancer diseases in the cat after skin tumors and lymphosarcoma. The histological features of feline mammary cancer resemble human mammary carcinoma more closely than do those of either the mouse or the dog. Pathological examination of feline mammary carcinoma has revealed virus-like particles in the cells that are not distinguishable from those seen in some types of mouse mammary tumors. Because of its similarity to human breast cancer, feline mammary carcinoma is a potential model for new forms of therapy; and indeed immunotherapy has been undertaken with some indication of success. One woman in 11 will develop breast cancer, which among the cancers is the greatest killer of women, making this a particularly important area of study. (42, 51, 77, 82, 105, 152)

Cardiovascular System

Although the cat is not usually the animal of choice for cardiovascular research, it has many cardiovascular disorders similar to those of humans, including cardiomyopathy, myocardial infarction, atherosclerosis, congenital cardiovascular disease, arterial thrombosis, and arteriosclerosis. Diseases of the heart rank first and cerebrovascular diseases third as leading causes of death in humans in the United States, making this a significant research area. (25, 93, 112)

Cardiomyopathy

Primary myocardial disease (cardiomyopathy) in the feline, a condition closely resembling the disease in humans, has been described (98). It is now believed to be a significant cause of disability and death in older cats.

Myocardial Infarction

Myocardial infarctions can be induced readily in the cat. The NIA report (98) notes that a survey of the literature published in the last 15 years shows more than 1,800 articles describing research involving the use of cats (and dogs) as models for this disease. Because most human deaths occur as the result of arrhythmias in the hours immediately following the myocardial infarction, this is a very important area of research. The cat (and dog) are also used to determine the effectiveness of drugs in limiting the area of necrosis following myocardial infarction and to aid in the development of infarct measuring techniques.

Atherosclerosis

Manning and Clarkson (99) have reported observing in the cat diet-induced atherosclerosis, a vascular disorder which may have its origin in congenital structure defects in the vascular system. Lesions in the human progress with age and may lead to cardiac infarction, stroke, gangrene, or aneurysm. Most older cats show lesions similar to those of man.

Headache

A December 1982 publication in *Clinical Science* by Hanson et al. (73) describes the effects, on respiration in the cat, of the sudden excitation of cerebral vascular nociceptors by carbon dioxide. They suggest their observation may be a way of studying the receptors responsible for headache.

Endocrine System

The study of comparative endocrinology, endocrinopathies, and hormone assay has been largely dependent on the use of laboratory animals. Newer radioimmunoassay procedures have replaced experimental animals in many instances. Animal model systems are used more now for hormone preparation and testing and the study of mechanisms involved in human endocrinopathies (106). Although the cat has not been the preferred subject for most endocrinological research, it has been used

to a limited degree in the study of diabetes insipidus and to a greater degree in diabetes mellitus.

Diabetes Insipidus

In 1938, Fisher et al. (53) used the cat in studies on diabetes insipidus, showing that the development of the disease in that species was dependent on the complete degeneration or removal of the neurohypophysis.

Diabetes Mellitus

Diabetes mellitus occurs spontaneously in the cat, the incidence being about 1:800. The condition is found more frequently in males. Diabetes mellitus is most commonly accompanied by amyloidosis (deposits of amyloid in the pancreatic islets, the islets which secrete insulin), and this relationship is being studied. This occurs with significant frequency only in humans and cats and is an important finding because it indicates that the cat is having a reaction similar to that of the human to the agent or the degeneration which has brought about this condition. Diabetes mellitus in both humans and cats is apparently associated with maturity-onset diabetes and may possibly have an hereditary basis. Hopefully, continued study of this condition in the feline will provide some of the information necessary for the alleviation of the human problem. (33, 83, 106, 108, 157)

Genetics-Heredity

Research on animal genetics is a well-established field of research with an experimental basis. Publications in the area of cat genetics are many (55, 85, 117, 129, 142). Cats suffer from a number of genetic defects, several of which have counterparts in humans, for example, retinal degeneration; esophageal achalasia; GM_1 gangliosidosis; amyloidosis; deafness; Chédiak-Higashi syndrome; congenital heart diseases, including vascular anomalies such as intraventricular septal defects and absence of aortic and pulmonary valves; hydrocephalus; spina bifida; cleft palate; congenital porphyria; deafness, mucopolysaccharidosis, persistent right aortic arch; oxalate calculi; hemophilia; Klinefelter's syndrome; and Niemann-Pick disease.

Studies on animals with the above conditions are often difficult, but they have provided information on the mechanisms of heredity, the dominance or recessiveness of the characteristics, and the evaluation of surgical and other procedures for correcting defects or alleviating symptoms.

Gangliosidosis

Cats share with humans various metabolic defects. One of these, a defect in lipid metabolism called GM_1 gangliosidosis, or lysosomal storage disease, has been studied by veterinary and pediatric researchers because of its similarity to the human disease. Recent research, in which properly functioning enzymes have been infused into diseased animals, has proved most encouraging. Children with certain types of gangliosidosis such as Tay-Sachs or Sandhoff's disease can be given supportive treatment only; and until now there was little promise of a therapy to promote their long-term survival. If the condition of the enzyme deficiency is allowed to persist, there is progressive, and eventually fatal, deterioration of the nervous system. This work on cats provides new hope for children with this disorder. (7–10, 45, 90, 133, 134)

Mucopolysaccharidosis I

Another naturally occurring disease in cats is α-L-iduronidase-deficient mucopolysaccharidosis, which can be compared with mucopolysaccharidosis I in man (76). Three clinical syndromes (Hurler, Scheie, Hurler-Scheie) are seen in man, each characterized by deficient α-L-iduronidase activity. The most severe form is Hurler's syndrome. It is characterized by corneal clouding, severe dysostosis multiplex, mental retardation, and death in the first decade of life. The disease in the cat resembles this syndrome most closely; clinical features include facial dysmorphia, corneal clouding, and skeletal abnormalities. This should be a useful model for studying the pathogenesis and therapy of lysosomal storage disease with central nervous system involvement.

Porphyria

In man, two forms of erythropoietic porphyria and three forms of nonerythropoietic (hepatic) porphyria occur. With the possible exception of the cat, domestic animals are affected with the erythropoietic type. The disease in the cat, which is inherited as an autosomal dominant trait, is characterized by biochemical features that overlap the various types of porphyrias found in man. Many of the clinical and biochemical features of feline porphyria resemble those of congenital erythropoietic porphyria. Porphyria in the cat may be a valuable model not only for the study of inborn errors of porphyria metabolism but also for the elucidation of control mechanisms of porphyria metabolisms and for studying induced porphyrias. (70, 71, 106)

Spina Bifida

The Isle of Man is said to be the origin of the Manx breed of cat, a delightful feline whose distinctive characteristics, including taillessness, are the result of a peculiar autosomal dominant trait. Severe congenital abnormalities, usually related to spinal lesions, result in the loss of a large percentage of kittens. The pathological characteristics of the Manx cat have been compared with spina bifida in man. Studies not only of spina bifida but also of the variable expression of simple autosomal alleles should find the Manx cat a very desirable and valuable animal model. It may also be of use in studies associating various abnormalities with behavioral characteristics (3, 4, 80, 86, 88). Additionally, Woodside et al. (156) have suggested that the Manx cat may be useful as an animal model for studying neurogenic visceral dysfunction associated with myelodysplasia.

Klinefelter's Syndrome and Chimerism

The male tortoiseshell cat serves as an excellent animal model for studies of both Klinefelter's syndrome and whole-body chimerism because of a sex chromosome abnormality that allows expression of both orange (yellow) and black coat color simultaneously in a male cat (coat colors are sex-linked in the cat) (15, 26, 27, 84, 106). The incidence of such cats is estimated to be 1 in 3,000 males. Klinefelter's syndrome in man is characterized by a number of conditions including gynecomastia and small testes without spermatogenesis. The presence of an additional X chromosome is recognized as being the cause of the disorder. Approximately 2 of 1,000 male human newborns have been shown to be affected. Studies of male mental patients have shown an incidence of 9 of 1,000. There is a need to study various aspects of this

syndrome such as increased height, reduced mental capacity, osteoporosis, and endocrine changes.

Chimerism is a term referring to the formation of a single individual from one or more lines of cells, cell lines which have their origin from different zygotes. (In mosaicism several lines of cells with different genetic content coexist, but they originate from a single zygote.) "Blood chimeras" are individuals (fraternal twins) in whom there was a prenatal exchange of bone marrow. Admixing of somatic cells results in "whole-body chimeras," individuals with intersex conditions, usually true hermaphrodites. Similar conditions, such as segmental pigmentary disorders, are found in both cats and humans.

Hemopoietic System

In the human, hematological manifestations are usually secondary to other diseases; this is also true in the cat. Any number of diseases may result in signs or symptoms of hematological illness. Although the cat may be a useful model of some of these hematological diseases, there is often difficulty with disease identification. (98)

Carnivore models of thrombosis and hemorrhagic diseases have been well described by the Institute of Laboratory Animal Resources in their *Second International Registry of Animal Models of Thrombosis and Hemorrhagic Diseases*, published in 1981 (44). Included are both spontaneous (hereditary and acquired) and experimentally induced disease models. The cat has been utilized in studies involving hemophilia A (classic hemophilia), hemophilia B (Christmas disease), factor XII or Hageman factor deficiency (Hageman trait), Chédiak-Higashi syndrome, arachidonate pathway of platelet function, and arterial thrombosis.

Chédiak-Higashi Syndrome

There is a great deal of interest in Chédiak-Higashi syndrome, an inherited disorder, in the cat and man, manifested clinically by partial oculocuteneous albinism, photophobia, increased susceptibility to infection and a tendency to hemorrhage. Although information gained from research on this disorder may very well be used in controlling this rare syndrome in humans, a great deal of useful information will be gained also by using cells and tissues from affected humans and animals to elucidate basic mechanisms and functions of tissues, cells, and organelles. (55, 125, 130)

Immune System

The importance of the immune system in the disease process is well established. The immune system of the cat has interested scientists for some time and has led to some very productive research in the areas of infectious diseases and cancer as discussed in other sections of this paper. In addition, cats have several immune disorders that bear great similarities to those of humans.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a disease primarily of women of child-bearing age. In the United States more than 16,000 people develop SLE each year. The overall incidence is about 1 in 2,000; and for women between 17 and 64 years of age it is about 1 in 700 (95). It may be acute and progress rapidly, or it may become chronic with sporadic occurrences of symptoms. The etiology is not known. A spontaneous disease occurring in cats resembles human SLE and has been the subject of a number of studies. Genetic factors and possibly a virus are thought to be involved in the development of feline SLE (131).

Gammopathies

In humans there occurs a set of disease syndromes characterized by elevated immunoglobulin production. These are called gammopathies. They are also referred to as plasma cell dyscrasias and are usually associated with tumors of immunoglobulin-forming cells such as multiple myeloma, Waldenström's macroglobulinemia, heavy chain disease, or lymphosarcoma. Functional plasma cell myelomas occur in the cat and, more frequently, in the dog. Recently, researchers have been studying with interest a serious and usually fatal viral disease of cats called feline infectious peritonitis (FIP) because of the elevated total serum protein level in cats with this disease. Although the etiologic agent of FIP has been identified as a coronavirus, the antigenic specificity of the elevated γ-globulin fraction in infected cats has not been determined. (34, 79)

Infectious Diseases (Viral, Bacterial, Parasitic)

The cat is susceptible to a great many infectious diseases. Vaccines and/or successful treatments are still not available for many of them. A partial list includes leukemia, infectious panleukopenia (feline distemper, feline enteritis), bacillary diarrhea, pneumonitis (coryza – *Chlamydia psittaci*), pneumonia, viral rhinotracheitis (herpesvirus), calicivirus infection (formerly picornavirus), reovirus, chronic sinusitis and rhinitis (result of severe respiratory disease), infectious peritonitis (coronavirus), infectious anemia (haemobartonellosis), coccidiosis, ringworm (dermatomycosis – several species of fungus), ectoparasites (mites and fleas), endoparasites (hookworms, tapeworms, roundworms), infectious neoplasms (primarily involving skin, mammary glands, bones), conjunctivitis (mycoplasma), and toxoplasmosis. Many of these diseases have been studied not only because they are a serious threat to the feline but also because they have counterparts in the human.

Haemobartonellosis

Hemolytic anemia caused by *Haemobartonella sp.* in the feline has been studied as a model for Oroya fever in the human (106).

Leukemia

The use of the cat as a model for leukemia has been discussed previously.

Toxoplasmosis

Toxoplasmosis is a disease of cats in which the cat serves as the primary host. Cats can acquire the infection through ingestion of oocysts (fertilized eggs) in raw meat, eating infected rodents or birds, or licking contaminated paws. The parasite, *Toxoplasma gondii,* reproduces in the cat's intestine, and the oocysts are deposited in the feces. These oocysts are extremely resistant to heat, cold, and drying and can retain their infectivity for long periods of time. Humans and other animals serve as the intermediate hosts for the parasite by ingesting the oocysts, either from raw meat or by contact with infected cat feces. Approximately 4,500 infants are born annually in the United States with congenital toxoplasmosis (*T.*

gondii). At least 200–400 of these have damage that requires permanent institutionalization. The disease is contracted through the placenta and occurs in about 50% of the pregnancies involving an infected mother. Clinically recognizable disease (often blindness) occurs in about one-fourth of these infants, and evidence suggests that a significant number of asymptomatic infants develop serious sequelae (visual, auditory, neurological, or intellectual impairment) later in life. Research is being conducted to develop diagnostic, therapeutic, and preventive measures for this infection.

Chlamydia

Among conditions caused by chlamydial infections in humans is salpingitis, the major cause of ectopic pregnancy and involuntary infertility in women. Chlamydia is the most common cause of eye infections and pneumonia in infants. More than 100,000 infants in the U.S. develop chlamydial infection each year. Urethritis and vaginitis have been produced in the cat with the feline keratoconjunctivitis agent, *Chlamydia trachomatis* (109). (Pneumonitis in the cat is caused by *C. psittaci.*)

Cholera

Cats have been used to study the adrenergic influence on intestinal secretion in cholera (24) and the effect of nicotinic and muscarinic receptor blockade on cholera toxin secretion (23).

Sporotrichosis

Humans who contract sporotrichosis do so as a result of having contact with vegetation or soil in which the etiologic agent, *Sporotrichum schenckii,* is growing as a saprophyte. A subacute or chronic disease results, with lesions distributed throughout the skin and subcutaneous tissue. Newborn cats are quite susceptible to experimental infection with the agent, and it can also be produced in adult cats. The course of the disease in cats is similar to that of the human disease. The cat model is of particular value in the assessment of antifungal agents (11).

Filariasis

Au et al. (6) have reported the detection of circulating antigens and immune complexes in both feline and human lymphatic filariasis.

Influenza

In 1970 cats were implicated as possible vectors in the transmission of A_2 Hong Kong influenza virus to humans (126). Experimental infection of cats showed them to be susceptible to the virus, and it was speculated that their close contact with humans might make them a more relevant animal to study in this context than some that were being considered.

Musculoskeletal System

As one of the most agile members of the animal kingdom, the cat can suffer trauma to its musculoskeletal system. The ability of this system to respond promptly in the healing and adaptive processes makes the cat an interesting clinical or research subject for obtaining new information on the musculoskeletal system.

Bone

Although man is one of the few animals to develop osteoporosis, all species appear to suffer bone loss in the aging process. In the cat, immobilization osteopenia, a very effective bone loss model, has been experimentally induced. In addition to bone loss in the cat, bone remodeling, preventative therapy, and restoration can be studied (98).

Hypervitaminosis A

Cats fed a diet consisting of only liver develop a chronic bone disease, deforming cervical spondylosis. This is comparable to the human condition, chronic hypervitaminosis A, which is caused by accidental overdose. In the human, as in the cat, skeletal changes occur during the growing period and subsequent to closure of the epiphysial plates. Studies have provided a better understanding of this condition and have shown that recovery can be expected. (29, 30, 94, 143, 155)

Nervous System

The central nervous system of the cat has been studied as extensively as the special sense organs (eye and ear). Cats have been one of the animals of choice used to map the pathways of the brain. This work has provided valuable information for the diagnosis, understanding, and possible therapy of many neurological disorders (schizophrenia, epilepsy, senile dementia). Only the nervous systems of the human and some subhuman primates have been studied in greater detail.

Brain

Mitruka et al. (106) list the cat as one of the animals which has been used for experimental purposes in gerontological research. Studies of catecholamine metabolism in the brain showed a loss of neurons in certain well-defined nerve tracts of cats to be less than 15%, comparable to that observed in humans (110).

"Split-brain" cats are an important example of brain research. Surgically, the two hemispheres of the brain are isolated so that each functions independently of the other. This, in effect, produces two brains in one skull. This technique, pioneered by Roger Sperry in the late 1950's, is now used by many behavioral biologists to learn how information is interpreted and applied by the two half-brains and by physicians and therapists who treat brain-damaged human beings in whom an accident or surgery has caused this "split-brain" condition (18). This research with cats and primates resulted in a Nobel Prize for Sperry in 1982.

Neuraxonal Dystrophy

Little is known about aging of the nervous system in animals. A need exists for animal models of these diseases that closely duplicate the neurological disorder. Cats exhibit spheroid swelling of terminal axons, known as neuraxonal dystrophy, a condition associated with aging in man. "The eminent position of domestic cats as subjects for morphophysiological studies of the CNS suggest that this species should be considered for use in systematic evaluations of aging on the nervous system" (98).

Spinal Cord Injury

The September 10, 1982, issue of *Science* carried an article by N. E. Naftchi entitled "Functional restoration of the traumatically injured spinal cord in cats by clonidine" (111). Naftchi has shown that long-term, chronic paralysis resulting from spinal cord injury in the cat has been reversed by the use of clonidine, an L_2-adrenergic receptor agonist. Preliminary studies in humans indicate that autonomic dysreflexia can be controlled and spasticity minimized. It is hoped that "this new approach to the restoration of function in the trauma-

tically injured CNS of mammals may find use in the immediate or delayed treatment of traumatic injuries to the spinal cord as well as brainstem lesions and cerebrovascular accidents."

Parkinson's Disease

Research involving cats and Parkinson's disease has also been reported in the literature (5, 154).

Optic

Examination of the feline eye with the ophthalmoscope is readily accomplished, as the cat can be trained to a variety of visual responses. Cats are good communicators if we learn to listen to them and read the signals that they send us. For this reason the cat has been invaluable in studies of vision problems. The cat's brain has been well mapped, and the relationship between visual problems, the development of the visual cortex, and the development of visual pathways has become well known. The cat has marvelous stereoscopic vision (depth perception) that enables it to hunt, climb, and play in the entertaining ways so familiar to us. The physiology of stereoscopic vision is now well understood because of studies in the cat (39, 54, 151). Development of the visual cortex was the subject of the research, in cats and primates, that led to a Nobel Prize for Hubel and Wiesel at Harvard. The structure of the anterior chamber of the cat's eye is similar to that of the human. It has been particularly useful in glaucoma therapy research because of the wide angle of the junction of the cornea and the iris. The cat has also been used, to some extent, in corneal transplantation work.

Central Retinal Degeneration

The cat has a number of visual problems, including central retinal degeneration, which may be either genetic or due to taurine deficiency. In humans, a form of retinal degeneration is observed called senile macular degeneration. A spontaneous lesion involving central retinal degeneration has been reported in the feline area centralis and has been characterized histologically as a loss of photoreceptors. Cats with this condition are said to show a reduced visual acuity which is proportional to the size of the lesion. A similar disease process results from taurine deficiency. Although no evidence exists of the precursor events accompanying human senile macular degeneration, the fact that the cat lesion is reproducible means that it is of value in studying photoreceptor degenerative processes. Additionally, as pointed out in the NIA report, it is of great importance that the photoreceptor degeneration in taurine deficiency can be not only halted but also reversed by the addition of taurine to the diet. (52, 68, 98, 128)

Hereditary Corneal Edema

Hereditary corneal edema has been described in the Manx cat (67). Early edematous lesions of the anterior corneal stroma progress to epithelial edema. Opacities characteristic in the human do not occur in the cat; however, as in anterior membrane dystrophies of humans, the epithelium shows spongiosis of the basal epithelial cells, large extracellular cysts, and a squamous epithelial surface. Other similarities to chronic corneal edema in human conditions are also observed in the cat.

Uveal Melanomas

Also described in the cat are uveal melanomas (1, 2, 113, 145). These tumors have been of great interest to scientists because it has been possible to grow them for a number of passages in in vitro cultures and because there is an apparent balance which can be achieved between the immune system of some cats and the growth of the tumor, with the immune system keeping the tumor in check. This research may provide further information on immunotherapy and cancer in humans.

Amblyopia

Cats have been widely used to study amblyopia (17, 153). Cats are agreeable to wearing corrective prisms, and as a result chronic studies can be done on these animals, enabling investigators to estimate problems involving binocularity in the vision of affected cats and to determine the effect of these changes on overall visual processes. Research has enabled the cat to contribute to the unscrambling of this difficult problem and to the better understanding of the human condition.

Cataract Surgery

Cataracts occur in domestic cats as well as in large wild felines. Surgery for cataracts is feasible for all members of the cat family (63–65, 144). Research on cats with cataracts has and will contribute to knowledge about lens structure and function as well as corneal healing after surgery.

Pollution-Environmental Health Hazards

The changes in our environment brought about by the ever-increasing population, technological developments, and industrialization have resulted in widespread pollution of natural air and water sources.

Methyl Mercury Toxicity

Cats have been used in research involving environmental contaminants such as methyl mercury toxicity (89, 106). The neurological signs associated with cerebral and cerebellar lesions are very similar to those of the human. In addition, the frequency of abortions and neuronal degeneration resulting from methyl mercury toxicity is similar in cats and humans.

Ciguatera Poisoning

Clark and Whitwell (31) report the use of cats in Brisbane, Australia, for bioassay of fish suspected of involvement of ciguatera (a nonbacterial icthyosarcotoxism) poisoning.

Mycotoxicoses

Lutsky and Mor (96) report the use of the cat for studying T-2 toxin-induced intoxication, a model of a human mycotoxicosis—alimentary toxic aleukia. The feline model has been very helpful in understanding the pathogenesis, therapy, and immune features of mycotoxicoses, as well as trichothecene-induced disease.

Respiratory System

The cat is susceptible to a variety of respiratory viruses and appears also to be quite sensitive to air pollutants. Nevertheless it has an adaptable and resilient respiratory system that makes it a good subject for comparative lung research.

Chronic Bronchitis

There have been reports of spontaneous chronic lung diseases in cats bearing some similarities to chronic bronchitis in humans. The etiologies, as in humans, are thought to be of infectious or allergic origin. Bronchiolar changes induced in cats produced an increase in goblet cells and the amount of intraluminal mucus (98).

Asthma

In the cat, a condition called "feline bronchial asthma" is a common clinical finding, with allergies and psychological stress thought to be possible causes (98).

Skin

The cat suffers from a number of skin disorders including eczema, dermatitis, alopecia, granulomas, and parasitic diseases. Ringworm is a skin infection also of human health significance because it is caused by the same organism in both humans and the cat. The acute reaction to certain parasitic infections appears to have an allergic basis.

Palisading Granulomas

According to Conroy (35), a relatively common condition in the cat is an entity identified as feline linear (or intradermal) granuloma. Spontaneous cutaneous and subcutaneous granulomatous inflammatory lesions occur associated with degeneration of collagen. The disease shares many clinical and pathological features with human granuloma annulare, also a palisading granuloma. In both species, the etiology is unknown. It appears that the cat may be a useful animal model in which to study the etiology and pathogenesis of human palisading granulomas.

Teratology

The abnormal development or congenital malformation of the embryo may be caused by intrinsic or extrinsic factors. Among the intrinsic factors are genetics, hormones, uterine environment, and metabolic and nutritional status of the mother. Extrinsic factors include drugs, chemical agents, radiation, and microbial agents. Viruses are probably the most common of the microbial agents. Cats, although they are not often the animal of choice for teratological studies, have been used. There is, in addition, a considerable amount of information available on spontaneous malformation, anatomy, and embryology of the cat (106).

Viruses

Feline ataxia virus has been shown to produce congenital infection, cerebellar hypoplasia and ataxia (87, 106).

Toxicology and Drug Metabolism Research

Toxicological studies are necessary to determine the safety of new drugs before they are administered to humans and/or animals. Cats are reported to be the animals used in 8% of toxicological studies (106).

Cats have been involved in the following areas of evaluation: drug toxicity, including drugs affecting the neuromuscular junction (muscle relaxants), parasympathetic-neuroeffector junction (autonomic nervous system), sympathetic neurojunctions (sympathetic nervous system), ganglionic block (hypertension – cat is animal of choice), and smooth muscles (perfusion of organs – histamine, oxytocin, and prostaglandins); analgesics (pain relief); anticonvulsants; anesthetics; antitussive agents (coughing); antitremor agents; spinal depressants (pain associated with spastic muscular contractions); psychotropic drugs (CNS stimulants and depressants – cats used very often in these evaluations, observing both their normal and drug-induced behavior); and drugs affecting blood vessels, heart, and kidneys (106). Chiou et al. (28) have reported a newly developed cat model for studying the mechanism of action of antiglaucoma drugs.

Summary

The continued improvement in the health of all species will always depend to some extent on the contributions of animals, cats included. Many feline diseases and conditions are still without means of prevention, cure, or treatment. In humans, solutions remain to be found in the areas of heart disease, hypertension, cancer, spinal cord injuries, diabetes, and chronic lung disease to name just a few; the aging population is confronted with its own array of complex diseases and disabilities.

Judging from the many references citing the cat as a research subject and from the great diversity of the research areas involved, it appears that the cat has been, is, and will continue to be a most valuable research subject. The contributions of the domestic feline to the markedly improved health of its own species over the years cannot be overestimated nor can its contributions to the improved health of man.

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Pound Animals for Research and Education

The scientific community has been placed on the defensive by its critics, who in recent years have become both articulate and politically effective. Proof of this can be attested by the ever increasing number of states and local communities now reversing previously adopted laws and policies that permitted the release of unclaimed pound animals for purposes of research and education.

By mid-1984 more than 80 bills had been introduced at some level of state or local government that would restrict the use or availability of animals (7). This alone suggests an erosion of public support on the issue of the use of pound animals and indicates an increasing effectiveness of the critics of animal research. As A.S. D'Ver (1) has aptly noted, the pound dog is becoming an "endangered species."

The pound issue first came to prominent public attention during World War II as research began to expand in response to a major federal commitment to enlarge the base of biomedical knowledge. Dogs and cats were among the species needed in increasing numbers, and scientific institutions turned to local pounds as a convenient, inexpensive, and reasonable source of supply.

Animal protectionists were as implacable then as they are today. Laws to prohibit animal experimentation, in general, and the use of stray dogs and cats, in particular, were being proposed in states, cities, and counties throughout the nation. The scientific community recognized then that an affirmative organized response was required to avert what could be a very serious threat to research should such legislation be enacted.

Accordingly, the National Society for Medical Research (NSMR) was organized in 1946 to foster public understanding of the needs and accomplishments of animal experimentation (2). State societies with similar purposes, such as the Medical Research Association of California, the Maryland Society for Medical Research, the Illinois Society for Medical Research, the New York Society for Medical Research, and others, also were established.

Educational materials were prepared and distributed nationally by NSMR. Working in cooperation with local groups, NSMR contributed to positive public education campaigns for passage of laws, ordinances, and local policies favorable to biomedical research. In the face of animal protectionist opposition, laws permitting the release of unclaimed animals for the purposes of research and education were passed in Minnesota, Iowa, New York, Massachusetts, and other states and Los Angeles, Chicago, Baltimore, Detroit, and other cities. Many counties also adopted similar permissive ordinances and policies.

The scientific community was successful on the pound issues of the 1940's and 1950's because it made a better case before the public than did the animal protectionists. The scientific community documented the moral purpose, explained the importance and value of animal experimentation in ways that made sense to the general population, and capitalized on the prevailing public respect for medical science. Polls conducted in 1948 by the National Opinion Research Center and the Minnesota Poll of Public Opinion both indicated that 85% of the general population was disposed favorably to providing unclaimed animals for research (5).

The situation in the 1980's, however, is radically different, and the problem is made more complicated by related veterinary medical and economic considerations, both of which bear upon the actual utility of pound animals in relation to their cost.

Wolfle (9) argues that high animal conditioning costs and the losses that result from intercurrent disease makes it uneconomical to use pound animals. Institutional breeding colonies have been suggested as a competitive alternative (8). The implied assumption is that this approach can provide better quality animals while avoiding the public policy problems associated with obtaining animals from pounds.

Perhaps some numbers may be instructive. Of the 200,000 dogs used in research and education annually in the United States, approximately 70% (140,000) are obtained either directly or indirectly from pounds. (Pounds kill approximately 13 million dogs annually.) The remainder of the dogs used are reared in laboratory colonies or by commercial breeders (6).

Vanderlip and Vanderlip (8) have projected a cost of $300 for a 4½ month-old mongrel pup weighing 40-50 lb. However, most investigators require mature animals, 1 year or older. At a daily laboratory colony maintenance cost of $2 per dog, an additional $450 must be added to the cost of rearing a dog to 1 year of age. Thus $750 is the real cost of a mongrel laboratory-reared dog weighing 50 lb. at 1 year of age.

If all or most dogs used for research in the United States had to be reared in laboratory or commercial colonies to the age of 1 year and the number needed was only 100,000 per year, the rearing cost alone would be approximately $75 million a year.

The cost for conditioned pound dogs is far less. For example, at the University of Michigan such dogs, purchased from a federally licensed dealer or conditioned at the University, presently cost less than $150 per dog. Nationwide in 1982 the prices ranged from $40 to $270 for conditioned dogs (3).

For uses requiring precise specification of genetic and environmental history, the higher cost of laboratory reared animals may be justifiable. But it makes no sense to require the use of purpose-bred animals in physiological and surgical research or for teaching purposes. For many such studies, pound animals are acceptable.

One also must question the rationale of those who would require the killing of two animals instead of one: the unclaimed animal from the pound that is to be killed in any case if it is not made available for research and

the animal that must be reared in the laboratory because scientific institutions are denied access to pound animals. A likely consequence of the loss of access to pound animals is that much meritorious research will have to be abandoned or will not be possible to undertake because the cost of appropriate experimental models will become prohibitive.

Furthermore, the argument that the scientific community can avoid the animals for research controversy by moving toward laboratory breeding is not supported by facts. Within weeks after a new law was signed in Massachusetts prohibiting scientific institutions from obtaining animals from pounds inside or outside of the state (4), several bills were introduced in the Massachusetts legislature to prohibit all animal experimentation. This was accompanied by full-page advertisements in prominent newspapers wherein the Massachusetts Society for the Prevention of Cruelty to Animals and the New England Anti-Vivisection Society proclaimed that the task was not yet complete.

There should be no doubt that the ultimate objective of the animal protection groups is the abolition of animal research. Recognizing that this is not attainable immediately, their interim objective is to secure severe and restrictive regulations, coupled with efforts to make animal research increasingly costly to conduct.

Michigan has been moderately successful in preventing the closure of its county pounds to scientific institutions. Since the Michigan Society for Medical Research was organized in 1980, animal protection groups have been defeated in four counties in efforts to overturn policies permitting the release by the pounds of dogs and cats for research.

This has been accomplished by mobilizing public opinion in these four communities, by providing factual information about animal research, and by demonstrating to the county supervisors that most of the citizens in their communities support the release of unclaimed animals for scientific purpose.

An underlying theme has been to demonstrate that animal research itself is a moral imperative. In the context of demonstrating that animal research contributes to human and animal welfare, a strong effort has been made to explain to the general populace how science works and how animals from pounds make their contribution to science.

This has helped to clarify the animal research issue in Michigan and has contributed to the public's ability to make the rational decision to be supportive. We in Michigan believe that public support of pound release policies is attainable, just as it was in the 1940's and 1950's. However, such support is not automatic in the 1980's. If the scientific community wishes to safeguard the public pounds as a source of supply for research animals, it then must follow the lessons of history and explain itself and its methods to the public, the ultimate arbiter of public policy.

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APS NEWS

Louis and Artur Lucian Award

APS council members, **Norman C. Staub,** professor of physiology and senior member of the Cardiovascular Research Institute at the University of California, San Francisco, has received the Louis and Artur Lucian Award in recognition of his contributions in the field of circulation research. Staub, a faculty member at UC-San Francisco and a member of the CVRI since 1958, was cited for his pioneering work on the microcirculation of the lung, in particular his studies over the last 15 years on pulmonary edema. Pulmonary edema is an abnormal accumulation of fluid in the lung that can cause victims to drown in their lung fluid. Staub has been using sheep since 1968 to help describe how lung liquid fluid accumulates. He developed a means of surgically implanting a plastic tube in a lymph duct in the chest to study the lymph draining from the lungs. The technique is used widely for studying lung liquid balance and allows long-term experiments on unanesthetized sheep. Staub and his associates are currently studying pleural effusions--the accumulation of liquid in the space between the lungs and the chestwall, and the manner in which liquid enters and leaves the air spaces in pulmunary edema. His laboratory is the first to measure the pressure in the tiniest blood vessels on the surface of the lung by puncturing them with microscopic glass tubes.

1984 Eli Lilly Award

APS member, **Alan Douglas Cherrington,** of Nashville, TN, has been honored by the American Diabetes Association as the recipient of the 1984 Eli Lilly Award for outstanding scientific achievement by a young investigator. This international award recognizes demonstrated research achievements in the field of diabetes. Dr. Cherrington, professor of physiology and associate director for research for the Diabetes Research and Training Center at Vanderbilt University School of Medicine, has made outstanding contributions to scientific understanding of glucagon, a body hormone which plays an intricate role in the development of diabetes. He was the first to directly demonstrate an important metabolic role for the basal glucagon secretion, and later showed that such secretion is largely responsible for maintaining hepatic glucose output after a prolonged fast. Further, he found that glucagon regulates only glucose supply, and not its disposal.

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APS Committees, Their Principal Functions and Membership (1984-85)

Animal Care & Experimentation

Maintains the APS "Guiding Principles in the Care and Use of Animals" by recommending changes for Council's consideration. Also provides other committees with consultation regarding animal experimental procedures and care.

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Career Opportunities in Physiology

Provides Council with information regarding availability and needs for appropriately trained physiological personnel and recommends measures to assure proper balance in the supply and demand for physiologists.

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Future Meetings

1985

FASEB Annual Meeting	April 21-26, Anaheim
Joint APS/The (British) Physiological Soc Mtg	Sept. 12-14, Cambridge (UK)
APS Fall Meeting	October 13-18 Niagara Falls/SUNY, Buffalo

1986

FASEB Annual Meeting	April 13-18, St. Louis
IUPS Congress	July 12-20, Vancouver, Canada

Proposed Amendment to the Bylaws for Publications Committee

The following amendment to the Bylaws to increase the number of Publications Committee members from three to five approved by Council will be offered for vote at the Society Business Meeting, Wednesday, August 29, 1984.

ARTICLE V. *Standing Committees*

SECTION 1. ***Publications Committee.*** A Publications Committee composed of ~~three~~ **five** regular members of the Society appointed by Council shall be responsible for the management of all publications of the Society. . . .

Centennial Celebration Committee

Utilizes the activities of the 1987 Centennial Year to make the scientific community and lay public aware of the history, nature and contribution of physiology and physiologists. This committee will phase out not later than 1989.

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Committee on Committees

Serves as an advisory committee to Council for the purpose of making recommendations for nominees to the standing committees.

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Ray G. Daggs Award Committee

Annually selects a member of the Society to receive this award in recognition of distinguished service to the Society and to the science of physiology.

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Education Committee

Conducts educational and teaching programs and develops teaching resource material that may be required by the Society. This includes naming tutorial lecturers, organizing teaching sessions and the refresher course conducted at APS meetings.

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Finance Committee

Reviews the proposed annual budget and fiscal plan for all Society activities and recommends a final budget and implementation plan to Council. Supervises the investment of the Society's financial resources subject to approval by Council.

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Honorary Membership Committee

Recommends to Council candidates for nomination to Honorary Membership, distinguished scientists who have contributed to the advancement of physiology.

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International Physiology Committee

Keeps Council informed of activities of the U.S. National Committee for the International Union of Physiological Sciences (IUPS), handles all matters pertaining to international physiological affairs on consultation with Council, and informs APS members of IUPS activities.

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Liaison with Industry Committee

Fosters interactions and improved relations between the Society and industry. Develops new ways that the Society and industrial concerns can interact in mutually beneficial ways.

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Long-Range Planning Committee

Advises and reports annually to Council and interacts with the Section Advisory Committee. Analyzes past and present societal performance; conducts periodic review of APS' relationship with other organizations; and devises specific goals and objectives pertinent to the future scientific mission of APS and American physiology.

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Membership Committee

Reviews and evaluates applications received from candidates for membership and recommends to Council the nominees for election to Regular, Associate, Corresponding and Student membership.

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Perkins Memorial Fund Committee

Selects recipients for visiting scientist family support awards and administers the Fund.

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Porter Physiology Development Committee

Selects recipients for visiting scientists and professorships; teaching and training fellowships, aimed at improving physiology departments of medical schools with predominantly minority enrollments. The Committee also supervises the administration of funds provided for this program.

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Program Executive Committee

Selects the scientific symposia and special sessions to be organized or supported by APS, develops policies regarding the conduct of scientific sessions and names the recipients of the Caroline tum Suden Travel Fellowship.

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Recommends to the Program Executive Committee scientific programs for APS meetings. Members of this committee also organize contributed abstracts into sessions, select session chairmen and introductory speakers, nominate candidates for the Caroline tum Suden Travel Fellowship.

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Public Affairs Executive Committee

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Public Affairs Advisory Committee

Consists of one member from each state who is responsible for reporting to the Public Affairs Executive Committee any legislation or regulation pertaining to biomedical research being considered or proposed by the state or any political subdivision thereof.

Members of this committee may develop a network of Society members within their states to assist in identifying pertinent proposed legislation or regulation and help to provide information to proper agencies regarding their effects on biomedical research, if enacted.

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APS Sections

How to Become Affiliated

In compliance with the Society's bylaws, a number of sections have been organized encompassing various physiological specialty interests. These sections advise the Society on matters of interest to the specialty represented by the section, assist the Society in organizing scientific meetings, and nominate individuals for membership on Society committees.

Membership in the sections is open to all members of the Society. However, the Statement of Organization and Procedures for each section establishes specific requirements for membership. APS members who wish to become affiliated with one or more of the listed sections should comply with the requirements noted following the named section. The reference shown beneath the name is the issue of *The Physiologist* where that section's Statement of Organization and Procedures has been printed.

Cardiovascular. 23(5): 5, 1980. Send a letter requesting affiliation to the Membership Services Department of APS.
Cell and General Physiology. 24(3): 35, 1981. Same as Cardiovascular.
Comparative Physiology. 20(6): 14, 1977. Indicate a primary or secondary Interest Area Code 10 on the Membership Records Questionnaire.
Endocrinology and Metabolism. 23(5): 8, 1980. Same as Cardiovascular.
Environmental, Thermal and Exercise Physiology. 20(6): 14, 1977. Indicate a primary or secondary Interest Area Code 13 or 14 on the Membership Records Questionnaire.
Gastrointestinal. 20(1): 5, 1977. Same as Cardiovascular.
History of Physiology, 27(4): 160, 1984. Same as Cardiovascular.
Nervous System. 21(3): 25, 1978. Indicate a primary or secondary Interest Code 25 on the Membership Records Questionnaire.
Renal Physiology. 20(2): 17, 1977. Attend Renal Dinner at the Spring Meeting.
Respiration Physiology. 23(5): 6, 1980. Indicate a primary or secondary Interest Code 32 on the Membership Records Questionnaire.
Water and Electrolyte Homeostasis. 25(3): 143, 1982. Same as Cardiovascular.

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Announcements

Seventh Conference on Biometeorology and Aerobiology

The Seventh Conference on Biometeorology and Aerobiology, sponsored by the American Meteorological Society, will be held in April/May 1985 in Phoenix, AZ. The conference will include sessions on aerobiology (encompassing modeling, microbiological, phytopathological, palynological, meteorological, and medical aspects), environmental physiology, physiological ecology, effects of past and future weather and climate on plants and animals, effects of pollutants on plant and animal acclimatization, and human mortality in heat and cold waves. *Abstract deadline:* 1 November 1984. *Information:* Kyaw Tha Paw U, Dept. of Land, Air and Water Resources, University of California, Davis, CA 95616 (916/752-1510).

New LSRO Study

The Life Sciences Research Office, FASEB, has initiated a review and evaluation of the human behavior and performance program of NASA's Life Sciences Division. The study will focus on review and analysis of current knowledge and research needs related to human performance requirements for space flight, human performance capabilities and limitations, psychophysiological aspects of performance in space, investigational methodology, and factors such as selection, training, and countermeasures. LSRO will constitute an ad hoc review group to assist in conduct of the study. *Information:* Dr. John M. Talbot, Senior Medical Consultant, Life Sciences Research Office, FASEB, 9650 Rockville Pike, Bethesda, MD 20814.

Scientific Steering Group on Food and Cosmetic Safety

The Life Sciences Research Office has appointed a Scientific Steering Group to oversee a major effort to examine various mechanisms for utilizing scientific expertise in the evaluation of issues in food and cosmetic safety. Under terms of a contract with the Center for Food Safety and Applied Nutrition, Food and Drug Administration, the Scientific Steering Group will assist LSRO in analyzing the utility and efficacy of various methods for obtaining from the scientific community pertinent research results, research needs, and technological advances that bear on questions of food and cosmetic safety. This 3-year effort will involve evaluation of several types of scientific questions. *Information:* Dr. Kenneth D. Fisher, Director, Life Sciences Research Office, FASEB, 9650 Rockville Pike, Bethesda, MD 20814.

Long-Range Planning Task Force Report

The Long-Range Planning Task Force was appointed in late 1980 and charged with the task "to consider all aspects of APS's activities they consider to be of importance relative to the well-being of our Society and the biomedical sciences in general, particularly during the next five years, and which hopefully will impinge favorably on the longer term, even less forseeable future. Certainly, APS-FASEB and other intersociety relationships should be considered. Problems of future meeting formats need not be excluded, although these aspects are being looked at intensively by the APS Future Meetings Task Force (the Vander Committee) and by Gene Yates' FASEB Thematic Meetings Committee.

The membership consisted of Drs. R. M. Berne (Chairman), A. P. Fishman, M. P. Hlastala, E. A. Hoffman, J. L. Kostyo, J. M. Marshall, and O. E. Reynolds (ex officio).

After several meetings, which included an interview with Dr. Robert Krauss, Executive Director of FASEB, the Task Force presented a preliminary report to Council at the FASEB meeting in 1982. Council discussed the recommendations of the Task Force and requested that the Task Force stay in operation for another year and gather input from the various sections of the APS. Although the information received was not up to the expectations of the Task Force, nevertheless there were sufficient data provided to enable the Task Force to obtain a consensus regarding some of the APS activities and to revise and add to the recommendations made the previous year. This report was made to Council at the FASEB meeting held in Chicago in April 1983.

However, there was insufficient time to adequately discuss the report, and a special meeting for discussion of the Task Force report (as well as other important subjects) was scheduled for November 1983. At this meeting the full report was presented, discussed, and acted on by the APS Council. The following constitute the Task Force recommendations and the responses (*italics*) and actions of the Council **(boldface).**

Standing Long-Range Planning Committee

The appointment of a standing Long-Range Planning Committee consisting of a recent Past President as Chairman, a current Council member, as well as young, senior, and minority physiologists was recommended. The Committee should be representative of the different specialty areas and have a broad geographical distribution. The maximum number of members should be nine with three of the current Task Force members serving one year, three appointments for two years, and three for three years.

Council approved the appointment of a 6-7 member Long-Range Planning Committee composed of a Past President as Chairman, a current Council member, and the balance of young and senior physiologists.

A motion was passed instructing the Committee on Committees to submit recommendations for Committee membership to Council in April.

Duties of the Long-Range Planning Committee

The Long-Range Planning Committee should, through subcommittees, closely follow the planning, actions, and results of the various activities of the Society. These include *1*) FASEB-APS interests; *2*) publications over the long haul; *3*) the development of APS sectionalization, particularly with response to "section journals"; and *4*) committees on public affairs, finance, etc. The Long-Range Planning Committee should also *1*) assure adequate input from the younger members of the Society; *2*) examine the efforts to increase the number of women and minority members; *3*) encourage membership or affiliate membership of sister societies such as Biomedical Engineers, the General Physiologists, the Biophysicists, and the Microcirculatory Society; and *4*) continually evaluate the expansion and composition of the Society.

Council agreed to prepare the Committee's charge before the Spring meeting. Continuing observation of the relationship between APS and FASEB should become part of the charge as well as a statement that Council may assign specific issues for which Council requires guidance. Also, it will meet with Council annually, and hopefully, it will be a "forward looking" and not only a "critical" Committee.

Section Advisory Committee

Establishment of a Section Advisory Committee to meet at least annually with Council and other APS committees for which there is a special requirement is recommended. Each section will appoint a representative to the Committee.

Council favored the concept of a Section Advisory Committee which would have input into the system through the Long-Range Planning Committee and Council. The Committee should be composed of Section Chairmen with the chair rotating alphabetically among them. It would be advantageous for Council to convene a meeting in St. Louis to provide an opportunity for the President to explain the purpose and to answer questions. Even though the Section leadership might change every year, it was agreed to be important to have the Chairmen on the Committee.

A motion was passed approving the appointment of a Section Advisory Committee, composed of Section Chairmen or the equivalent with an alphabetical rotation of the chairmanship, to interact with the Long-Term Planning Committee and to meet annually with Council at the Spring meeting.

Correction

In the Long-Range Planning Task Force Report published in the June 1984 issue of *The Physiologist* several paragraphs were transposed and is printed in its entirety to avoid confusion.

A motion was passed that the Sections nominate their Chairmen or their Secretaries if they do not have Chairmen who will be the member on the Section Advisory Committee for his/her term as Chairman.

It was agreed to send a letter to the Section Chairman announcing the formation of the Section Advisory Committee to interact with the Long-Range Planning Committee and Council and extend an invitation to meet with Council at the Spring Meeting in St. Louis on Sunday morning, April 1. The first charge to the Committee will be consideration of a uniform structure for the various Sections. Also at this time, the mechanism for selecting the Committee Chairman can be determined.

Membership Committee

It is recommended that the composition of the Membership Committee consist of a representative from each of the Sections, which would screen the applications and make recommendations to the Membership Committee for final action. This would obtain appropriate representation of the various sections on the Committee.

Council decided not to accept this recommendation of the Long-Range Planning Task Force *pointing out that the recommendations for Committee appointments can be advanced by the Section Advisory Committee. Currently, the Committee on Committees asks Sections to submit nominees for committee service. However, when the Membership Committee reviews the criteria for membership, it can take this item under advisement. This, too, may be an appropriate item for discussion at the Section Advisory Committee Meeting in April.*

Term of APS President

It is recommended that the term of the APS president can be extended to two years, thereby permitting greater continuity in the planning and development of new policies and programs.

At the request of Dr. Fishman, each member of Council expressed his views concerning a one-year versus a two-year term as President. The discussion resulted in **passage of a motion that the President's term continue to be for one year.**

FASEB

The Society's relationship with FASEB seems to have stabilized. Therefore, no action was taken at this time, but it is recommended that a continuing periodic review be conducted. One member suggested that *Federation Proceedings* be made available to students at a low cost (ca. $5.00/year).

As previously mentioned, a statement to this effect will be incorporated in the charge to the Long-Range Planning Committee.

Meetings (FASEB and APS)

Following the recommendation of the Yates Committee regarding thematic meetings, and continuance of two meetings per year for the present, the Task Force recommends the following:

1) The Fall meeting have no limit on the number of abstracts per member and should have symposia, refresher courses, tutorials, and state-of-the-art lectures by young and senior physiologists. Joint meetings with other societies should be encouraged. However, the question of continuation of Fall meetings should be reevaluated after the campus meetings are held in 1984 and 1985.

2) The Spring meetings with FASEB be restructured along different lines. It is recommended that a member can either coauthor or sponsor one paper, as was the practice until two years ago. A suggested format for the Spring meeting was prepared by the Task Force and is on file in the APS Headquarters. (A copy will be provided on request.) Details of restructuring the program of the APS Spring meeting must be worked out with the Section Advisory Committee and the Program Executive Committee with input from the Council and the Executive Secretary (practical and financial aspects).

Council found the overall proposed format for the Spring meeting very attractive and liked the concept of the morning plenary sessions and symposia with afternoon paper and poster sessions. The most important aspect of the concept is to assemble all physiologists via the plenary session and business meeting with more high-quality symposia. It was reaffirmed that the Bowditch Lecture and Past President's address would be presented at the Spring meeting.

The proposed restructure of the Spring meeting as presented by the Task Force was approved by Council, and the Program Executive Committee was asked to implement the new format with the following modifications: Simultaneous paper and poster sessions in the afternoon and on Monday with spillover on Friday if necessary, and the restriction of one sponsored or coauthored paper per member.

There was discussion of the composition of the Fall meeting and that it not get short shrift but continue to have tutorials, refresher courses, symposia, state-of-the-art lectures, and having a plenary session would be desirable. The Fall meeting is regarded by some physiologists as important as the Spring meeting. Therefore, as long as there is an interest in the Fall meeting and it does not become a liability, it is to be continued.

An outline for the Fall meeting was prepared by the Task Force at the request of Council and is also available on request.

No action was taken on the Task Force's recommendation to "encourage FASEB to increase the number of Gordon Conference type meetings in areas of interest to physiologists and keep the APS abreast of the FASEB's plans."

Robert M. Berne, Chairman

35th Annual Fall Meeting of the American Physiological Society

Hyatt Regency Hotel
Lexington, Kentucky

August 26-31, 1984

For information on Fall Meeting registration, call the APS Fall Meeting Office (301)530-7010.
For information on the meeting program, call the Membership Services Department (301)530-7171.

Special Events

Bowditch Lecture
Tuesday, 4:30 PM
Hyatt Regency, Patterson A/B/C
Glycoprotein Hormone Genes:
Hormonal Regulation of Expression
William W. Chin, Harvard Medical School

APS Past President's Address and Business Meeting
Wednesday, 9:00–10:30 AM
Hyatt Regency, Patterson A
Alfred P. Fishman

APS History of Physiology Section Business Meeting
Wednesday, 12:00–1:30 PM
Hyatt Regency, Linda Neville Room

Evening Social Events
Special Lecture
Monday, 7:15 PM
Hyatt Regency, Regency Ballroom
A Surgeon's View of a Race Horse
R. W. Copelan, Paris, KY

Opening Reception
Monday, 8:00–10:00 PM
Hyatt Regency, Regency Ballroom

APS Banquet
Tuesday, 6:45–9:00 PM
Hyatt Regency, Regency Ballroom
A Physiologist in Space
Astronaut F. Story Musgrave

Picnic at Spindletop
Wednesday, 6:00–9:30 PM
Spindletop Faculty Alumni Area

Open House at the University of Kentucky
Thursday, 5:00–7:00 PM

Comparative Physiology Mixer
Thursday, 8:00–10:30 PM
Hyatt Regency, Washington Room

Refresher Course, Tutorials, Symposia, and Workshop Sessions

Monday PM
Refresher Course: Anaerobic threshold

Tuesday AM
Tutorials
The central respiratory pattern generator
Pulmonary gas exchange
Information processing in the retina: review and recent advances

Symposia
Life at reduced water activities
Vasoactive agents in control of the mesenteric circulation

Tuesday PM
Tutorials
Cellular mechanisms of gastric acid secretion
Biophysics of taste
Integration of surface digestion and transport

Symposium
Intrarenal hemodynamics

Wednesday PM
Tutorials
Microcirculatory response to anesthetics
Neural regulation of cold-induced vasodilation
Fluid and electrolyte exchange during exposure to cold

Symposia
Neural control of renal function
Loaded breathing: load compensation and respiratory sensation
Session I: Sensory mechanisms

Thursday AM
Symposia
Loaded breathing: load compensation and respiratory sensation
Session II: Respiratory sensations
Alteration in microcirculatory function during hypertension
Current topics in neuroendocrine control of gonadotropin
Chronophysiology and athletic performance

Workshop
Integrative study in physiology and medicine

Thursday PM
Symposia
Loaded breathing: load compensation and respiratory sensation
Session III: Motor responses
Quantitative approaches to the study of cardiovascular regulation

Workshop
Physiologist's approach to age-dependent changes in function

Sessions with Associated Abstracts by Day

(APS Tutorials, Symposia, and Refresher Course sessions are not listed, since abstracts are not required.)

5.1

ACID-BASE EFFECTS ON ALDOSTERONE SECRETION. K.J. Radke, R.E. Taylor, Jr., and E.G. Schneider, Dept. of Physiol., Univ. TN. Ctr. Hlth. Sci., Memphis, TN 38163.

The effects of acidosis and alkalosis on angiotensin II (AII)-, potassium (K)- and ACTH-stimulated aldosterone (aldo) secretion were examined in isolated, perfused canine adrenal glands. During perfusion with normal Ringer's-Bicarbonate solution gassed with 95% O_2 and 5% CO_2 (pCO_2 = 39.4 ± 0.4 mm Hg (SE); pH = 7.40 ± 0.00), infusion of AII (60 pM) or ACTH (10 pM) or elevation of perfusate [K] to 5.4 mM caused 2.0- to 4.0-fold, sustained increases in aldo secretion. During each of these stimulated conditions, lowering pCO_2 of the perfusate to 14.3 ± 0.6 mm Hg (pH = 7.82 ± 0.01) inhibited aldo secretion. In contrast, elevating pCO_2 of the perfusate to 64.5 ± 0.8 mm Hg (pH = 7.18 ± 0.00) further increased AII- and K-stimulated aldo production but only slightly influenced ACTH-stimulated aldo secretion. These effects were observed to occur within 20-40 minutes. For each stimulated condition there was a significant ($P<0.05$) correlation between the log of fractional aldo secretion and [H]. Fractional aldo secretion is the ratio of aldo secretion during the final period of acidosis or alkalosis to that just before the change in pCO_2. These results suggest that acidosis and alkalosis, induced by changes in pCO_2, have a direct effect on the response of aldo secretion to physiological stimuli. Thus, acid-base status must be considered when evaluating the control of aldosterone secretion. (Supported by USPHS Gr. HL-27749 and HL-07339).

5.2

STEROIDOGENIC AND PRESSOR RESPONSE TO ANGIOTENSIN II AND ANGIOTENSIN III IN ANDROGEN TREATED DOGS. D.K. Roman*, J.E. Carroll*, T.L. Goodfriend* and R.E. McCaa. VA Hospital and University of Wisconsin, Madison, WI 53705 and the University of Mississippi Medical Center, Jackson, MS 39216

Androgens increase angiotensin binding and stimulate aldosterone production in bovine adrenal glomerulosa cells. This study was designed to evaluate the effects of androgens on angiotensin II (A-II) and angiotensin III (A-III) *in vivo*. Eight conscious dogs were pretreated with dexamethasone and captopril, and infused with four graded doses of A-II and A-III for one hour each, on consecutive days, while plasma aldosterone concentration (PAC) and arterial pressure (AP) was monitored. Dogs were given IM injections of either testosterone hemisuccinate in DMSO or DMSO every 12 hours. Two days later the A-II and A-III infusions were repeated. PAC (ng/dl) and AP (mm Hg) values ±S.E. before and after each hour of A-II infusion before androgen treatment were 14.8±6.1, 101±4; 23.7±6.4, 103±4; 41.7±6.8, 121±4; 67.7±8.7, 139±3; and 97.1±12.5, 149±1, and PAC and AP values during A-III infusions were 3.9±0.4, 86 ±4; 14.8±3.1, 94±3; 42.0±6.8, 105±3; 92.5±6.7, 126±4; and 95.7 ±14.8, 133±3. PAC and AP values after androgen or vehicle treatment did not vary statistically with A-II or A-III infusion. In contrast to the enhanced angiotensin binding and aldosterone production observed in bovine adrenal glomerulosa cells treated with androgens, our study demonstrated that androgens failed to alter the aldosterone or pressor response to A-II or A-III in conscious dogs. (Supported by NIH Grant HL-09921.)

5.3

PLASMA A II AND ADH OF DUCKS IN RELATION TO BODY FLUID PARAMETERS AND TO THE STATE OF ADAPTATION TO SALT STRESS. Eckhart Simon and David A. Gray*. Max-Planck-Institute, W.G. Kerckhoff-Institute, D-6350 Bad Nauheim, F.R.G.

Birds with salt glands may exhibit physiological variations of their osmoregulatory state much larger than in many mammals. We have studied plasma AII (^{5}Val-angiotensin II) and ADH (arginine vasotocin) of freshwater (FW) and 2% saline (SW) adapted ducks (RIA method) in relation to their body fluid parameters; plasma osmolality: Π, plasma sodium: |Na|, and hematocrit: Hct. At control conditions in which the sodium spaces of SW and FW ducks are known to be identical, the SW ducks - and the FW ducks, in parenthesis - exhibited average levels of Π: 312 (295) mOsm.kg^{-1}, |Na|: 150 (142) meq.l^{-1}, Hct.: 40 (40) %, AII: 115 (35) pg.ml^{-1}, ADH: 12 (5) pg.ml^{-1}. In SW ducks AII was positively correlated with |Na| ($2P<0.01$). SW ducks loaded intravenously with 1.6 ml.min^{-1} of 250 mOsmolal saline retained some fluid and AII decreased at decreasing |Na|. When the saline was replaced by hyposmotic glucose solution, salt and some water were lost and AII increased at decreasing |Na|. FW ducks responded to the 250 mOsmolal saline infusion with a drop in AII. Prolonged infusion of hyposmotic glucose solution tended to increase AII. In all conditions ADH paralleled Π which was closely correlated with |Na| ($r > 0.9$). It is concluded that both, plasma tonicity and body fluid volume, control AII and ADH in ducks, however, with a preponderance of the volume parameter in the control of AII and of the tonicity parameter in the control of ADH.

5.4

VASOPRESSIN, ALDOSTERONE, AND RENIN RESPONSES TO HEAD-OUT WATER IMMERSION IN CONSCIOUS DOGS. J.A. Krasney, G. Hajduczok*, S.K. Hong, and J.R. Claybaugh. SUNY-Buffalo, NY 14214 and Tripler AMC, Honolulu, HI 96859.

Vasopressin (UadhV) and aldosterone (UaldoV) excretion and plasma renin activity (PRA) were determined during head-out water immersion (WI) at 37°C in the quadruped position in conscious dogs. The dogs were hydrated initially with 0.45% NaCl solution (2% body weight) and urine was collected via a Foley catheter. Animals were studied either during 200 min in air, or during 100 min in air followed by 100 min of WI. UadhV, UaldoV, and PRA were determined at 20 min intervals to assess the intergrated response over the entire period of WI. During WI, there were increases in urine flow (214%), sodium excretion (191%), and osmolal clearance (85%) while there was no change in potassium excretion or free water clearance. UadhV, UaldoV, and PRA did not significantly change from the air control values. We conclude that WI in the quadruped position does not provide a sufficient stimulus to influence humoral mechanisms involved in blood volume regulation in the conscious dog. (Supported by NIH grant PO1-HL28542)

5.5

RENAL RESPONSES TO HEAD-OUT WATER IMMERSION IN CONSCIOUS DOGS AFTER CARDIAC DENERVATION. G. Hajduczok*, S.K. Hong, J.R. Claybaugh, and J.A. Krasney. SUNY-BUFFALO, NY 14214 AND TRIPLER AMC, Honolulu, HI 96859

Dogs were subjected to chronic total extrinsic cardiac denervation (CD) via an intrapericardial approach using the technique of Randall et al. (J. Surg. Res. 29: 101, 1980) in order to determine the role of cardiac afferent nerves in the renal response to head-out water immersion (WI). All CD animals showed no renal response to left atrial balloon inflation in the conscious state. After initial hydration with 0.45% NaCl (2% body weight), urine was collected during 100 min in air followed by 100 min of WI at 37°C in the quadruped position. As compared to a group of sham-operated dogs (S), the CD animals showed a similar increase of urine flow (S=214%, CD=231% above control values). However, the magnitude of the natriuretic response was attenuated significantly after CD (S=191%, CD=44% above control $U_{Na}V$ values). The S dogs showed an increase in osmolal clearance (+85%), while free water clearance was unchanged. By contrast, the CD dogs showed no significant change in osmolal clearance, but free water clearance increased by 126% above control values. These data indicate that cardiac receptors are important in determining the nature of the renal response to WI but that extra-cardiac mechanisms can initiate a sustained diuretic response. (Supported by NIH grant PO1-HL28542.)

5.6

PLASMA AND BLOOD VOLUME FOLLOWING ANTEROVENTRAL THIRD VENTRICLE PERIVENTRICULAR ABLATION AND EXTRACELLULAR FLUID VOLUME DEPLETION. Steven L. Bealer. Dept. Physiol., Univ. Tenn. Ctr. Hlth. Sci. Memphis, TN 38163

Electrolytic ablation of the periventricular tissue of the third cerebral ventricle (AV3V) results in expanded total extracellular fluid volume, contracted plasma (PV) and blood (BV) volumes, and significantly greater increases in plasma concentrations of renin, aldosterone, and corticosterone following volume depletion. These experiments characterized the effect of furosemide treatment on PV and BV in AV3V-lesioned animals to determine if further reduction in vascular volume occurs following this treatment. AV3V-lesioned and control-operated animals received furosemide injections (150 mg/kg) and sodium-free chow or saline injections and regular rat food. One week after injection, PV and BV were determined by calculation of radioisotope dilution of ^{125}I-labelled serum albumin. PV and BV were significantly smaller in volume-replete, AV3V-lesioned rats (12.0±.4 ml; 22.0±.9 ml) than in volume-replete control-operated rats (13.1±.4 ml; 24.1±.6 ml). Volume depletion significantly reduced PV and BV in both control-operated (10.9±1.3 ml; 20.3±.7 ml) and AV3V-lesioned (10.3±.8ml; 19.6±1.5 ml) animals. These data demonstrate that furosemide treatment decreases PV and BV in animals with AV3V ablations. This further decrease in vascular volume may account for their exaggerated responses in plasma concentrations of renin, aldosterone, and corticosterone. (Supported by USPHS HL-25877).

5.7

GASTRIC DISTENSION INCREASES RENAL PELVIC CONTRACTION RATE IN THE HAMSTER. L.N. Reinking, M.D. Hall* and K.B. Miller*. Millersville University, Millersville, PA 17551

Anesthetized (Inactin, I.P., 150 mg/kg), female golden hamsters were infused with 1% lissamine-green to give the urine a contrasting color and the activity of the renal pelvis was monitored with a fiber optic scanner. This system detected the passage of colored boluses of urine as they were propelled through the renal papilla by contractions of the renal pelvic wall. In control animals, the renal pelvic contraction rate declined with time. This trend was reversed ($p<.001$) when a small quantity of water (0.5% body wt.) or only a plastic tube was introduced into the stomach. Introduction of water into the stomach while the duodenum was ligated produced similar results. Infusion of hypotonic solutions into the hepatic portal vein had no effect on contractions. Previous studies have shown that renal pelvic contractions influence kidney function. Distension of the stomach is one of the first effects of oral volume loading. Thus, it is possible that the stomach, via connections to the urinary system, acts as an "early warning device" and aids in the elimination of oral fluid loads. (Supported by AHA, Lancaster Pa. Chapter)

5.8

BLOOD ACTIVATION OF ATRIAL NATRIURETIC FACTOR (ANF). Andrzej Januszewicz,* Francis E. Cole,* Allan A. MacPhee,* Nick C. Trippodo. Alton Ochsner Medical Foundation, New Orleans, LA 70121

ANF is comprised of high (HP) and low (LP) molecular weight peptides. The HP (10,000-30,000) are activated (enhanced biological activity) by in vitro proteolytic cleavage, which converts them to the LP (<10,000). To determine if in vivo activation (conversion) of the HP can occur in the blood, rat HP were partially purified by gel filtration in 1.0 M acetic acid, lyophilized and reconstituted in oxygenated Krebs-Ringer bicarbonate buffer (KRBB). One ml of fresh rat blood containing no anticoagulants was incubated with the HP at 37°C for 2 min. After centrifuging, the supernatant was fractionated on Sephadex G-75 in 0.1 M acetic acid. Natriuretic activity (NA) was determined by bioassay in anesthetized rats. In contrast to the results following incubation of the HP in KRBB alone, which showed that 90% of the NA remained in the HP region, the NA of the blood-treated HP eluted exclusively in the LP region indicating complete conversion. The blood converting factor was inhibited by heparin but not by EDTA. Blood containing EDTA was separated into plasma, erythrocytes, lymphocytes, and platelets. Conversion of the HP to the LP occurred only after incubation with the platelets. No platelet conversion of the HP occurred after boiling the platelets, in the absence of calcium, or with heparin in the incubation medium. The results indicate that circulating HP are readily activated in the blood stream by a platelet-associated, calcium-dependent converting factor. Supported in part by NIH (HL 29952) and Ciba-Geigy, Limited.

5.9

CHARACTERIZATION OF A BIOASSAY FOR NATRIURETIC ACTIVITY OF RAT ATRIAL TISSUE EXTRACTS. Michael D. Johnson. Department of Physiology, W.Va. Univ. Med. Ctr., Morgantown, WV 26506.

The present investigation was conducted to characterize a bioassay for the natriuretic and diuretic effects of extracts of atrial tissue. A pool of crude atrial extract (AE) was prepared from atria collected from decapitated Sprague-Dawley rats. Right and left atria were homogenized in ground-glass tissue grinders in 5 volumes of phosphate-buffered saline (PBS), pH 7.2. The homogenate was boiled for 10 minutes and then centrifuged for 20 min at 27,000 g at 4° C. Aliquots of the supernatant were stored at -70° C. Samples of AE were injected intravenously into Sprague-Dawley bioassay rats in a total volume of 0.5 cc PBS. Injected doses ranged from 27 to 432 µg of AE protein. Analysis of the results indicated that the most sensitive and reproducible parameter to determine natriuretic activity of AE was not a change in $U_{Na}V$ (the parameter used most frequently by other laboratories to detect atrial natriuretic activity), but was instead the log of the ratio of the experimental and control values for $U_{Na}V$. With the use of the latter parameter as the response variable, the bioassay is capable of detecting natriuretic activity in 27 µg of crude AE protein, an amount roughly equivalent to the quantity of protein derived from 1/16 of the atrial tissue of one rat. (Supported by a grant from the West Virginia University Senate Research Committee.)

5.10

EFFECTS OF ARGININE VASOPRESSIN ON CARDIAC OUTPUT. Udom Tipayamontri,* David D. Young, Zahij G. Nuwayhid, and Robert E. Scott.* Univ. of Miss. Med. Ctr., Jackson, MS 39211

Administration of arginine vasopressin (AVP) reduces cardiac output (CO) in a variety of settings. This may be the result of an effect of the hormone on the heart and/or on the circulatory system. To determine the magnitude of the cardiac effect of AVP, cardiac function curves were determined in 8 conscious instrumented dogs before and after AVP concentration was elevated by 48 hr of dehydration, 30 min infusion of AVP at 1.0 mU/kg/min, or 4 days of AVP infusion at the same rate. Cardiac function curves were determined by infusing 3% body weight of Tyrode's solution iv over a 30 sec period while monitoring right atrial pressure (RAP) and CO (measured by an EM flow probe around the ascending aorta). The Tyrode's infusion increased RAP to at least 16 mmHg. Plotting RAP vs. CO produces the cardiac function curve. Under control conditions resting CO averaged 137±11 ml/min/kg and increased to a maximum of 255 ml/min/kg as a result of forcing RAP to 16 mmHg. During the dehydration period resting CO was 82% of the control value ($p<.05$) and the max value was 84% of the control max ($p<.05$). During acute AVP infusion the resting value was not different from the control value although the max was only 69% of the control max ($p<.01$). Chronic AVP infusion did not affect either the resting or max portions of the curve. These data demonstrate that AVP in the high physiological range has an important negative effect on the pumping ability of the heart. Supported by AM11675.

5.11

RENAL DENERVATION LOWERS BLOOD PRESSURE IN THE ONE KIDNEY LOW SODIUM HYPERTENSIVE RAT. R.C. Vari*, R.H. Freeman, J.O. Davis and W.D. Sweet*. University of Missouri, Columbia, MO

Unilateral nephrectomy of sodium restricted rats produced a sustained elevation in systolic blood pressure (SBP) that was reversed by renal denervation. Comparison of SBP is shown over time for normal sodium (NS), low sodium (LS), low sodium renal denervated (LS-DEN), and low sodium sham denervated (LS-SHAM) rats. * = $P<0.05$, day (0) is SBP six weeks post nephrectomy.

	Pre	wks				days			
Group	Neph	2	4	6	Group	0	3	7	10
LS (36)	109 ±2	140* ±2	136* ±2	133* ±2	LS-DEN (16)	133 ±2	114* ±2	116* ±2	119 ±3
NS (11)	114 ±2	124 ±3	122 ±2	123 ±2	LS-SHAM (11)	133 ±2	126 ±2	124 ±3	122 ±3

Renal denervation was verified by a 96% decrease in kidney norepinephrine content. Six weeks after nephrectomy, plasma renin activity was significantly elevated ($P<0.05$) in LS rats compared to NS rats (4.5 ± 1.5 vs. 1.3 ± 0.2 ngAI/ml/hr), and was unaffected by renal denervation. No difference was observed between LS-SHAM and LS-DEN groups in urinary Na^+, K^+, and fluid excretions. These results suggest that the renal nerves partially mediate the sustained elevation in SBP in this experimental model of hypertension.

6.1

HISTAMINE H_1 RECEPTOR ANTAGONISTS INHIBIT PROSTAGLANDIN-INDUCED RENAL VASODILATION. **Robert O. Banks and Eugene D. Jacobson. Dept. of Physiology and Biophysics, Univ. of Cincinnati, College of Medicine, Cincinnati, OH 45267-0576**

Effects of histamine antagonists on prostaglandin-induced renal vasodilation were studied. Mongrel dogs (5/group) of either sex (15-25 kg) were anesthetized with pentobarbital (25 mg/kg). The dogs were given saline (0.25 $ml \cdot min^{-1} \cdot kg^{-1}$), left renal blood flow (RBF) was measured with a flow probe and agents were infused directly into the renal artery. When RBF was stable one of the prostaglandins (PG) was infused until RBF had attained a plateau (5-10 min). The infusion was stopped and RBF allowed to restabilize. An infusion of the histamine H_1 antagonist chlorpheniramine (chlor, 10^{-5}M/min) was then begun. After 10 min an infusion of chlor + a PG was then initiated and RBF allowed to plateau (5-10 min). RBF values ($ml \cdot min^{-1} \cdot g^{-1}$) are given (means ± SEM, *=p<.05 compared to PG alone). Similar results were obtained with the H_1 antagonist pyrilamine (10^{-5}M/min, n=5) + PGE_2 whereas 10^{-5}M/min cimetidine (H_2 antagonist, n=5) had no effect. We also found that H_1 antagonists do not markedly affect acetylcholine-induced renal vasodilation. Thus, our data suggest that exogenous PG-induced renal vasodilation may be mediated by intrarenal histmine release. Supported by NIH 29021.

	Control	PG	Chlor	Chlor+PG
PGE_2(0.1 µg/min/kg)	2.65±.30	4.99±.50	2.79±.21	3.50±.30*
PGI_2(0.01 µg/min/kg)	3.19±.33	4.40±.37	3.04±.30	3.99±.29*
PGE_1(0.1 µg/min/kg)	3.04±.33	5.59±.41	2.74±.28	4.60±.41*
PGD_2(0.1 µg/min/kg)	2.89±.43	5.60±.38	2.87±.25	4.67±.42*

6.2

ROLE OF GLUCAGON DURING PROTEIN-INDUCED ELEVATIONS IN RENAL BLOOD FLOW AND GLOMERULAR FILTRATION RATE. A.J. Premen, J.E. Hall, M.J. Smith* and P. Rushing*. Dept. of Physiol. & Biophys., Univ. Miss. Med. Cntr., Jackson, MS 39216

Glucagon (GLN) has been suggested as a mediator of protein-induced elevations in renal blood flow (RBF) and glomerular filtration rate (GFR). The aim of this study was to examine the quantitative importance of GLN in mediating these postprandial changes in renal hemodynamics in chronically instrumented conscious dogs. Data were taken from 3 fasted dogs in which 4 protocols were run in each: normal protein control meal (C); high protein meat meal (M); somatostatin infusion + meat (S+M); and GLN infusion. Following C, RBF and GFR were slightly elevated (<10%) while arterial plasma GLN was no different from its average control of 27±8 pg/ml over a 3 hour period. M produced large increases in RBF (38%) and GFR (37%) and plasma GLN markedly increased to a 3 hour average of 69±6 pg/ml (3-fold increase). During S+M, RBF and GFR failed to increase while GLN fell to undetectable levels. When S was stopped, GLN rose to 80±12 pg/ml over the next hour (2.8-fold increase); yet, RBF and GFR increased by only 14 and 8%, respectively. 3 ng/kg/min GLN (iv) increased plasma GLN to 87±3 pg/ml (3-fold increase); yet, RBF and GFR rose by only 4 and 5%, respectively. These data indicate that while a high protein meal (meat) does increase plasma GLN, the rise in GLN is not great enough to produce a significant elevation in RBF or GFR and thus, cannot account for protein-induced elevations in RBF and GFR.

6.3

DOPAMINE RECEPTORS (DR) IN DOG INTRARENAL ARTERIES (IRA). Robin A. Felder*, John J. Worthington* & Pedro A. Jose. Dept. of Peds., Georgetown Univ. Med. Ctr., Wash., D.C. 20007

Dopamine induces renal vasodilatation in the mature canine. Low affinity DR in renal artery and high affinity DR in glomerulus have been reported but no measurements have been made on the arterial segments interposed between these two structures. These experiments characterize for the first time DR in dog IRA by radioligand binding using ^{3}H-haloperidol (H). IRA were dissected and homogenized. Specific H binding was defined as the difference in binding in the presence and absence of 30 uM cis-flupenthixol (a potent dopamine antagonist). Kinetic analysis revealed a binding site that saturated in 3 min. and remained at steady state for over 1 hr. The dissociation constant (K_d) calculated from kinetic data was 8 nM. Competition studies were consistent for DR: haloperidol>trifluperidol>LY-141865>Ym-09151>cis-flupenthixol>(-)-propranolol>prazosin> SKF-82526, and stereoselective: (+)-apomorphine>>(-)-apomorphine. Rosenthal plots were biphasic. The high affinity DR site had a K_d of 2.3±1.0 nM and a maximum receptor density (B_{max}) of 19.5±5.0 fmol/mg protein (±SEM, n=5). For the low affinity site the K_d was 31.8±1.7 nM and the B_{max} 92±20 fmol/mg protein (n=5). These results suggest that canine IRA contain specific DR. The specific DR-2 antagonist Ym-09151 and the DR-2 agonist LY-141865 were more potent than the relative DR-1 selective antagonist cis-flupenthixol and DR-1 agonist SKF 82526 respectively suggesting that the predominant DR in the canine IRA is of the DR-2 subtype. (supported by HL 23081)

6.4

GFR AUTOREGULATION DURING LONG-TERM REDUCTIONS IN RENAL PERFUSION PRESSURE. J.E.Hall and J.-P. Montani*, Univ. Miss. Med. Ctr., Jackson, MS 39216, USA

This study examined renal autoregulation and regulation of electrolyte excretion during chronic servo-controlled reductions in renal artery pressure (RAP). In 9 normal dogs, RAP was decreased to 73±1 mmHg and maintained at that level for 7 days with an electronic servo-controlled aortic occluder. After 1 and 7 days of decreased RAP, GFR was autoregulated at 94±2 and 87±3% of control, while effective renal plasma flow (ERPF) decreased to 80±6% of control and filtration fraction (FF) increased to 112±4% of control. Na excretion decreased markedly on the first 2 days of decreased RAP, but then returned to control due to decreased absolute and fractional Na reabsorption. Mean arterial pressure (MAP) above the renal arteries increased gradually from 97±2 to 135±5 mmHg after 7 days. In 5 dogs in which AII formation was blocked with captopril and circulating AII was held constant by continuous iv infusion of 1-2 ng/kg/min of AII, servo-controlling RAP at 74±1 mmHg for 6 days caused similar changes in MAP and renal function, except that ERPF was better autoregulated, FF did not change significantly, and the increase in the MAP was not as rapid. When RAP was servo-controlled a few mmHg below the autoregulatory range in normal dogs, escape from Na retention did not occur and malignant hypertension developed after 1-4 days. Thus, GFR autoregulation can be sustained for at least 7 days and may play an important role in protecting against severe Na retention and malignant hypertension.

6.5

RENAL INTERSTITIAL PRESSURE DURING INHIBITION OF LOOP OF HENLE SODIUM TRANSPORT. J. A. Haas, J. P. Granger, J. C. Burnett, Jr.,* F. G. Knox, Dept. of Physiol.,Mayo Clinic and Foundation, Rochester, MN 55905

Previous studies have suggested an association between renal interstitial hydrostatic pressure (P_I) and sodium reabsorption by the loop of Henle. To determine the cause and effect relationship between loop of Henle sodium reabsorption and P_I, the present study was performed to determine P_I after direct inhibition of loop of Henle sodium transport with the intravenous infusion of furosemide (F) (2 mg/kg/min) or bumetanide (B) (.04 mg/kg/min) in the dog.

	P_I	P_C	P_T	MAP	FE_{Na}	GFR	RBF
	- - - - - mmHg - - - - -				%		ml/min
C (n=5)	7±.5	14±.7	21±1	112±3	.51±.13	25±3	263±36
F	7±.8	15±.7	28±1*	115±3	15.1±2.9*	26±2	248±26
C (n=6)	7±.4	13±.4	20±1	109±1	.31±.10	26±4	254±18
B	7±.3	15±.3*	31±.4*	108±.4	6.2±.80*	32±4	253±17

*p<.05 vs control (C)

Furosemide and bumetanide infusions increased tubule pressure and fractional sodium excretion (FE_{Na}%), but did not change interstitial pressure. These studies indicate that direct inhibition of loop of Henle sodium transport and increases in tubular pressure are not necessarily associated with increases in renal interstitial hydrostatic pressure. (Supported by NIH HL14133)

6.6

EFFECTS OF DIETARY NaCl ON REGIONAL BRAIN RENIN ACTIVITY (BRA) IN NORMAL RATS. Claude P. Genain*, Glen R. Van Loon, Jan H. Downs* and Theodore A. Kotchen* University of Kentucky, Lexington, KY 40503.

To evaluate the effect of dietary NaCl on brain renin, BRA was measured in selected brain areas in 3 groups of male Sprague-Dawley rats (n=8/group) after 10 days of normal (NS), high (HS), and low (LS) NaCl diets. BRA was measured through angiotensin I generation in supernatents of sonicated samples obtained from saline-perfused brains (<0.2% v/w plasma contamination), incubated with excess rat angiotensinogen at pH 7.0 to reduce nonspecific protease activity and with effective angiotensinase inhibitors. BRA had an heterogeneous distribution with the higest levels found in neuroendocrine glands (pg/mg protein/h, mean ± SD):

	Anterior Pituitary	Posterior Pituitary	Pineal Gland	Olfactory Bulbs	Plasma Renin
NS	9.6±4.8	8.6±4.3	16.6±8.6	1.1±0.5	6.3±3.5
HS	6.4±4.0	5.6±2.7	11.0±3.5	1.1±0.4	3.5±1.9
LS	21.0±9.3*†	15.4±13.2†	21.3±11.6†	2.0±0.8*†	22.7±11.2*†

p<0.05: *, LS vs NS; †, LS vs HS;

In amygdala, hypothalamus, striatum, frontal cortex, and cerebellum, BRA was lower and was not affected by dietary NaCl. Brain contents of nonspecific proteases and angiotensinogen were also not affected by dietary NaCl. Thus, similar to renal renin, BRA is stimulated by dietary NaCl deprivation in selected areas of the brain, both within and outside the blood brain barrier.

6.7

DIETARY SODIUM DEFICIENCY POTENTIATES THE EFFECT OF PGF2-ALPHA AND OTHER AGENTS ON IN VITRO RENIN RELEASE IN THE RAT. G. A. Lopez, A. Ebneshahidi*, A. Bell*, S. Jaramillo*, K. Khalighi*, N. Lopez*, S. Rivas* and J. Tantisira* California State University, Los Angeles, CA 90032.

This study investigated whether the effect of PGF2-A and other agents on in vitro renin release (RR) is correlated with changes in tissue cyclic AMP content (T-cAMPc), and if it can be altered by dietary sodium manipulation. At 10^{-5}M, PGF2-A significantly stimulated both RR and T-cAMPc in renal cortical slices from sodium deficient (SD) rats but only T-cAMPc in slices from sodium loaded (SL) animals. PGF2-A at 10^{-6}M and 10^{-7}M, and the PG-precursor arachidonic acid (AA) at 10^{-5}M, were ineffective in both groups of slices. The PG-synthetase inhibitor indomethacin (I, 10^{-4}M), reversed the RR responses to a previously ineffective 10^{-5}M dose of AA in both groups of slices, and to 10^{-6}M and 10^{-7}M PGF2-A doses in the SD group and 10^{-5}M PGF2-A in the SL group, without altering T-cAMPc. The phosphodiesterase inhibitor theophylline ($T_{2.7}10^{-4}$M), reversed the RR responses to PGF2-A doses of 10^{-7}M in the SD group and 10^{-5}M in the SL group and to 10^{-5}M AA in both groups, without affecting T-cAMPc. Added alone, both T and I increased RR but not T-cAMPc. These data suggest that: 1) sodium deficiency enhances the RR responses to certain PGF2-A doses, and that changes in T-cAMPc may mediate this effect; and 2) at the doses used, both T and I increase RR by a pharmacological effect independent of T-cAMPc changes, which is potentiated in the SD state. (Supported by NIH #5-S06-RR08101).

6.8

DIFFERENTIAL EFFECTS OF NACL AND ALBUMIN VOLUME EXPANSION ON PLASMA RENIN ACTIVITY IN THE RAT. J. N. Lorenz*, W. J. Welch* and C. E. Ott. Univ. of Kentucky, Lexington, KY 40536

It has previously been shown that a 35% plasma volume expansion (VE) with NaCl or a 100% plasma volume expansion with albumin can cause an acute suppression of plasma renin activity (PRA) in the rat. However, whether the inhibition seen with NaCl is dependent upon volume as well as a tubular mechanism is not clear. To evaluate the contribution of volume expansion to the suppression of PRA by NaCl infusion PRA was measured in two groups of NaCl depleted rats before and after equivalent expansion with either NaCl or albumin. The NaCl group was plasma volume expanded by 50.6 ± 5.1% and the albumin group was plasma volume expanded by 54.6 ± 3.4%. PRA decreased in rats expanded with NaCl (15.3 ± 2.2 to 7.8 ± 1.5 ng/ml/ hr; $p < .05$) while no significant change was seen after expansion with albumin (9.91 ± 0.72 to 8.2 ± 1.02 ng/ml/hr). Glomerular filtration rate increased within each group after VE ($p < .05$) but was not different between groups before or after VE. Blood pressure was not significantly different after VE in either group. Sodium excretion increased significantly in both groups after VE ($p < .05$). Chloride excretion increased significantly after NaCl VE ($p < .05$) but was not significantly changed after albumin VE. These results support the hypothesis that suppression of PRA by 50% volume expansion with NaCl is mediated by a tubular mechanism independent of a volume dependent mechanism.

6.9

ADRENERGIC MECHANISMS FOR RENIN RELEASE IN THE PENTOBARBITAL ANESTHETIZED RAT. R. H. Freeman and A. Goff*, University of Missouri, Columbia, Missouri 65212.

This study was designed to assess the participation of adrenergic mechanisms in the elevation of plasma renin activity (PRA) in male, Sprague-Dawley rats anesthetized with sodium pentobarbital (50 mg/Kg,i.p.) and with vascular catheters placed in a carotid artery and a jugular vein. Control measurements of blood pressure (BP) and heart rate (HR) were made for 30 minutes prior to ganglionic blockade (hexamethonium bromide; 30 mg/Kg, iv); additional measurements of BP and HR were continued for 40 minutes following ganglionic blockade. A blood sample for the measurements of PRA and plasma norepinephrine (NE) concentration was obtained immediately prior to hexamethonium administration; a second blood sample was obtained 30 to 35 minutes later. Results: Ganglionic blockade produced an initial decrease in both the HR and the BP. BP fell from a control of 138 ± 5 to 78 ± 4 mmHg ($p<0.05$) within 5 minutes after blockade, but then returned to 125 ± 5 mmHg by the end of the experiment. Control PRA correlated positively with baseline plasma NE ($r=0.56$). After ganglionic blockade, NE decreased from 301 ± 48 to 173 ± 32 pg/ml ($p<0.01$) and PRA fell from 5.9 ± 0.5 to 2.5 ± 0.5 ng AI/ml/hr ($p<0.01$). These data indicate that the sympathetic nervous system partially contributes to the elevation of PRA in the pentobarbital anesthetized rat.

6.10

CHANGES IN THE PROPORTIONS OF RENIN FORMS IN THE GOLBLATT HYPERTENSIVE RAT. Francis M. Sessler* and Richard L. Malvin. Department of Physiology, The University of Michigan, Ann Arbor, MI 48109

Six forms of renin have been described in rat kidney. Different stimuli resulted in secretion of unique profiles of those forms. We studied their secretion in the 2-kidney, 1-clip Goldblatt hypertensive rat (GHR). Renal venous blood, kidney homogenates and incubation media from cortical slices were subjected to isoelectric focusing. In all samples tested, six peaks of renin activity were found with isoelectric points at pH 5.70, 5.55, 5.30, 5.15, 4.90, and 4.80. The quantity of renin activity for each form was expressed as a percentage of the total recovered from the gel. In control kidneys the profile of renin in the homogenate and that released by the slices were identical. However, in plasma, the percentage of renin focusing at the more basic pH's was decreased. This is in agreement with other work showing that the liver removes the more basic forms more rapidly than the acidic forms. The clipped kidney of GHR secreted, both in vivo and in vitro, a profile of renin forms that was significantly different from both the contralateral unclipped kidney and from control kidney. The difference was expressed by an increase in the secretion of the more acidic forms by the clipped kidney. The change in the secretory profile of renin may be a reflection of a change in synthesis or storage of those forms. Supported by NIH Grant HL-18575

6.11

EFFECTS OF ANGIOTENSIN ANTAGONISTS, α-BLOCKADE, AND CAPTOPRIL ON THE ANGIOTENSIN PRESSOR RESPONSE IN THE BULLFROG. G. A. STEPHENS and R. A. Harper* Univ. of Delaware, Newark, DE 19716

We examined the effects of three angiotensin analogues, phenoxybenzamine and captopril on the pressor response to angiotensin I (AI), angiotensin II (AII) and norepinephrine (NE) in the bullfrog, Rana catesbeiana. Injection of AI and AII at 0.25, 0.5 and 1.0 ug/kg, or NE at 3 ug/kg elicited dose-dependent rises in blood pressure. [Sar1,Ile8] AII (10 ug/kg/min) blocked all doses of AI and AII. [Sar1,Ala8] AII blocked only the highest dose, and [Sar1,Thr8] AII produced no blockade. Captopril (0.1 mg/kg bolus + 0.5 mg/kg/hr) significantly reduced the response to AI, but not AII or NE. Phenoxybenzamine (5-10 mg bolus + 1 mg/kg/hr) blocked NE, and partially inhibited (28-51%) the pressor effects of AI and AII. These results demonstrate that 1) [Sar1,Ile8] AII is a potent angiotensin antagonist in the bullfrog, 2) captopril is an effective converting enzyme inhibitor, and 3) a portion of the angiotensin response can be inhibited by α-receptor blockade and is apparently due to catecholamine release. (Supported by NHLBI HL-25084.)

6.12

STUDIES ON RENIN-ANGIOTENSIN SYSTEM AND ITS RELATIONSHIP TO ARTERIAL PRESSURE CHANGES DURING HEMODIALYSIS. J. Colina-Chourio, G. Parra*, R. García* and B. Rodríguez-Iturbe*. Nephrology Service, Hospital Universitario and Department of Physiology, Facultad de Medicina, Universidad del Zulia, Maracaibo, Venezuela.

To evaluate the variations observed on the renin-angiotensin system due to hemodynamic changes that occur during hemodialysis, thirteen patients with chronic renal failure treated with periodic hemodialysis with (n=9) and without (n=4) ultrafiltration (UF) were studied. Sitting arterial blood pressure (BP) and heart rate were measured by a continuous non-canulating monitoring system and plasma renin activity (PRA, ng/ml/h) was measured before and after 2,4 and 6 hours of hemodialysis. Body weight (BW) was measured before and after 6 hours of hemodialysis. There was a decrease in BW in both groups being, as expected, more intense in the UF group. Both systolic and diastolic BP showed a gradual decrease reaching a plateaux at 4 hours (mean decrease 10% of initial value). PRA showed opposite changes to those of BP, increasing progressively from 3.65 ± 2.92 before dialysis to 7.02 ± 4.98 at 4 hours (up to 200%) and 6.99 ± 4.98 at 6 hours. There was no significant difference in the BP and PRA values between the UF and non-UF patients, probably due to the limited number of observations. These results suggest that during hemodialysis PRA responds physiologically to the hemodinamic changes that occur during this therapeutic procedure. (Supported by CONICIT Venezuela and Asociación Amigos del Riñón del Estado Zulia, Maracaibo, Venezuela).

7.1

LIMITATIONS ON THE CAPACITY OF THE SYSTEMIC CIRCULATION TO MAINTAIN CARDIAC OUTPUT WITHOUT THE PARTICIPATION OF THE RIGHT VENTRICLE. Paul A. Spence*, Karim A. Jabr*, Victor Yap* and Tomas A. Salerno*, University of Toronto, Toronto, Ontario Canada, M5B 1W8 (Spon: C. David Ianuzzo)

To study the capacity of the systemic circulation to maintain the cardiac output (CO) without participation of the right ventricle (RV), ventricular fibrillation (VF) was induced in 8 pigs and the systemic circulation was supported by a left heart bypass (from left atrium to aorta). In 4 animals the pulmonary circulation was unaltered and a CO equal to the pre-VF value could be achieved by volume loading to increase right atrial (RA) pressure to 20-30 mmHg. The circulation could be maintained for 15 minutes without difficulty. Pulmonary hypertension was produced in 4 additional animals and they were subjected to similar procedures. Baseline CO could not be reproduced until the RA pressure was increased to between 35 and 50 mmHg. It was not possible to sustain the CO in these animals. These results indicate that the systemic circulation can maintain an adequate CO during left heart bypass and VF when the pulmonary vasculature is unaltered, but RV function is necessary when the pulmonary vascular resistance is increased.

7.2

EFFECT OF ACUTE CORONARY ARTERY LIGATION ON LEFT VENTRICULAR PERFORMANCE, OXYGEN CONSUMPTION, AND MECHANICAL EFFICIENCY. H.M. Voogjarv* and J. Grayson. University of Toronto, Toronto, Ontario M5S 1A8.

A right heart bypass was used to examine the effect of acute left anterior descending coronary (LAD) ligation on mechanical efficiency (ME) of the canine left ventricle (LV). ME was calculated from the ratio of LV external work (EW) to its oxygen consumption (MVO_2). EW was calculated from the product of mean arterial blood pressure (ABP) and cardiac output (Q). MVO_2 was determined from the product of coronary sinus blood flow (CSBF) and arterio-coronary sinus O_2 difference ($(a\text{-}cs)O_2$). Acute LAD ligation resulted in a 21% decrease in CSBF which was partially compensated by an 8% increase in $(a\text{-}cs)O_2$. MVO_2 decreased by an average of 15%. Left ventricular external work, on the other hand, decreased by 24% as a result of a 15% decrease in Q coupled with a 12% decline in ABP. As the fall in EW exceeded the fall in MVO_2, calculated ME was observed to decrease by an average of 10%. These data show that acute ligation of the LAD leads to decreased MVO_2 which is associated with a decrease in LV performance. This effect is further exacerbated by a decrease in cardiac mechanical efficiency.

(Supported by the Ontario Heart Foundation)

7.3

STABILITY OF ISOLATED BLOOD PERFUSED EMPTY BEATING PIG HEART. Randall Jones*, R.M. Engelman, and W. Dobbs. University of Connecticut Health Center, Farmington, CT06032. Six hearts from young domestic pigs, were isolated from the systemic circulation and perfused with oxygenated blood via the Langendorff method for 180 minutes using an extracorporeal pump oxygenator. Periodic measurements of isometric left ventricular developed pressure, ΔP, dp/dt and oxygen extraction were taken to indicate the stability of this preparation and to serve as control measurements. A second group of five hearts was subjected to the same procedure with the exception that Starling curves were determined at 0, 60, 120 and 180 minutes by perfusing the left atrium and measuring aortic flow and left atrial pressure. In both groups isometric developed pressure and dp/dt declined from initially high values over a 30 minute period to values which remained relatively stable for the remainder of the perfusion interval. However, the slope of the Starling curves declined exponentially over the entire perfusion interval from 51.0 to 1.4 ml/mmHgmin, after 180 minutes of perfusion. Oxygen extraction was 0.66 in the working mode and 0.30 in the isometric, nonworking mode. Thus, the use of Starling curve determinations to indicate changes in cardiac performance of the isolated heart over a period of 180 min unmasked a decline in the heart's ability to function which was not obvious from measurements of isometric left ventricular pressure. Thus, the isolated blood perfused empty beating heart is a highly supported preparation and changes in its ability to function as a pump are not always revealed by measurements of isometric pressure development.

7.4

SERIAL ASSESSSMENT OF CENTRAL HEMODYNAMICS IN GROWING PREMATURE INFANTS USING IMPEDANCE CARDIOGRAPHY. W.R. Sexson, R.W. Gotshall, and D.S. Miles. Depts. of Pediatrics and Physiology, Wright State Univ., Dayton, Ohio 45404

Stroke volume (SV) and cardiac output (Q) were measured using impedance cardiography in 12 premature infants. Serial measurements were taken every 3 to 4 days while the infants were at rest using a Minnesota 304B impedance cardiograph. Weights ranged .82 to 3.8 kg. There was no clinical evidence of a patent ductus arteriosus or of congenital heart disease. Spot electrodes were used on the forehead and leg to generate a constant electric field. Mylar strip electrodes were used circumferentially around the neck and semi-circumferentially at the xyphoid to detect impedance changes. SV and Q increased linearly with weight. The following regression equasions were obtained for selected parameters:

Y =	m X	+ b	r	p
SV =	.81(wt)	+ .51	0.523	<.01
Q =	127(wt)	+ 78	0.567	<.01
Z_o =	$-1.1(L_{2-3})$	+ 49	0.113	NS

These data compare favorably to the limited results of others obtained invasively. Impedance cardiography appears to be a promising technique with which to non-invasively measure SV and Q in even very tiny neonates. (Supported in part by the Miami Valley Chapter of the American Heart Association.)

7.5

NEW TECHNIQUES FOR ISOLATION AND PERFUSION OF THE TOTAL WORKING GUINEA PIG HEART. S.F. Yaffe* and C.T. Liu. US Army Med Res. Inst. of Infect. Dis., Ft Detrick, Frederick, Md. 21701.

Two techniques for isolated perfused heart have been used extensively for studying cardiac hemodynamics and metabolism: one allows the left heart to perform work (Neely), while the other produces no work (Langendorff). The present study was to isolate and perfuse a heart with different approaches, enabling both ventricles to work. Guinea pigs (500-700 g) were anesthetized and maintained with a respirator during thoracotomy. The heart (~2.5 g) was perfused with Krebs-Henseleit solution in situ via the aorta after the pulmonary artery (PA) was cut. Pulmonary vessels were ligated and lungs removed before the heart was excised. The superior vena cava (VC) and the coronary sinus (CS), via the inferior VC, were cannulated for perfusing the right atrium (RA) and collecting the coronary flow. The CS was blocked from RA by a suture around the cannala. The PA and left atrium were connected. Isolated hearts (N=3) were stable for 4-6 hrs and the following data were obtained:

RA filling pressure(mmHg)	5.0	Coronary R. (dyne.sec/cm^5)x10^5	1.8
Aortic pressure (mmHg)	45.0	Cardiac output (ml/min/g)	17.5
Aortic flow (ml/min/g)	12.5	Heart rate (beats/min)	222.0
Coronary flow (ml/min/g)	5.0	Stroke vol. (ml/beat/g)x10^{-2}	7.9

With standardized surgical procedures, this preparation is suitable for comparing cardiac functions between control and experimental animals. Further, effects of drugs, toxins, plasma or tissue extracts may be evaluated in the total working heart.

7.6

TRANSIENT HEMODYNAMIC RESPONSES TO CIRCULATORY STRESS IN NORMAL MALE SUBJECTS OF DIFFERENT AGES. J.J. Smith, J.A. Barney*, C.J. Porth, L. Groban*, A. Stadnicka* and T.J. Ebert. VA Medical Center, Wood, WI 53193 and Medical College of Wisconsin, Milwaukee, WI 53226

Transient circulatory stress responses are reportedly indicative of autonomic function. We studied the effect of age on the initial responses to graded headup tilt (HUT) and graded Valsalva maneuvers (VALS). Heart rate (HR), stroke volume index (SVI) and thoracic blood volume (TBV) (transthoracic impedance) were monitored in normal males, 20 to 29 yrs (YM), 40 to 49 yrs (MM) and 60 to 69 yrs (OM). At all HUT levels, the HR rise began within 2 secs, peaked at 6 to 12 secs and receded to a relative plateau. The peak HRs increased with the HUT angle but the initial HR rise and the return to control were delayed in OM. SVI and TBV declined promptly in all groups but the TBV decrease was least in OM. During the VALS, OM showed lesser changes and greater delay in the HR responses and lesser decreases in TBV.

The results indicate that 1) significant age differences exist in the transient responses of human subjects to HUT and VALS stresses and 2) the age differences may be due to functional hemodynamic as well as autonomic factors.

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7.7

OXYGEN TRANSPORT AND CONSUMPTION VS. CARDIAC OUTPUT AT DIFFERENT HEMOGLOBIN CONCENTRATIONS. W.Y. Moores*, D.C. Willford, E.P. Hill, R. Bellamy, W.H. Heydorn*, and P.O. Daily*. UCSD School of Medicine, La Jolla, Ca, 92093 and Letterman Army Institute of Research, San Francisco, Ca, 94129

Peripheral O_2 delivery and consumption were studied in 5 anesthetized, surgically instrumented pigs on cardiopulmonary bypass while lowering the cardiac output (pump flow) at two hematocrit concentrations (30 and 15). Arterial and venous O_2 contents (CaO_2 and CvO_2) and lactate concentrations [L] were measured as pump flow (Q) was decreased. Whole body O_2 consumptions (VO_2) were calculated by the Fick principle: $VO_2=Q\cdot(CaO_2\cdot CvO_2)$. VO_2 and [L] were plotted vs. total O_2 transport ($TOT=Q\cdot CaO_2$). At the high hematocrit the plots showed 2 distinct regions: a TOT independent region above 10.7 ml O_2/min/ kg and a TOT dependent region below this value. We refer to the transition between the 2 regions as the "critical O_2 transport" and quantitate it by fitting 2 straight lines to the data and calculating the intersection of the 2 line segments. The two regions were also identified in the same animals at a hematocrit of 15%. However, the critical O_2 transport was significantly lower (7.3‡ 2.7 ml O_2/min/kg vs. 10.7‡ 2.7 ml O_2/min/kg; P 0.05) at the lower hematocrit than at the higher hematocrit. We speculate that the decrease in critical O_2 transport at the lower hematocrit might be due to a better distribution of blood flow.

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7.8

EFFECT OF CHRONIC NOREPINEPHRINE INFUSION ON FUNCTION OF THE HYPERTROPHIED HEART. F.M. Siri*,R.M. Smith*(SPON: R.T. Dowell) Dept. of Physiology, Univ. of Hawaii, Honolulu, HI, 96822.

Depressed myocardial function is frequently reported in the chronically pressure-overloaded heart. This is often accompanied by depleted myocardial norepinephrine (NE) stores, as well as elevated plasma NE, suggesting that circulating NE may be providing critical inotropic assistance in such cases. A study was undertaken to assess possible beneficial effects of chronic subpressor NE infusion on myocardial function of rats subjected to abdominal aortic constriction (AC). Four groups received an initial operation consisting of AC or sham constriction, along with implantation of an Alzet osmotic minipump to intravenously infuse either NE (0.05 mcg/kg/min) or vehicle. After 7 days, heart size and function were evaluated. Left ventricular mass increased by more than 30% in both AC groups. Compared to the double-sham group, only the NE-infused AC group had greater peak stroke work index ($P < 0.05$) during volume loading. In addition, both NE-infused groups had steeper function curves than the double-sham group ($P < 0.05$ in each case). There was also evidence of greater wet lung weights ($P < 0.01$) in the NE-infused AC group, compared to the AC group not receiving NE infusion. These data suggest that in the AC model, this NE infusion leads to increased performance and to decreased compliance of the left ventricle. The increased performance may be at the expense of elevated left ventricular end diastolic pressure and pulmonary congestion, thus the therapeutic value of a chronic NE infusion in this model is uncertain.

7.9

HEMODYNAMIC RESPONSE TO ALFENTANIL IN ANESTHETIZED DOGS. N. D. Kien*, J.A. Reitan*, D.A. White* and C.H. Wu* (SPON: E.M. Renkin). Dept. of Anesth., Univ. of Ca., Davis, Ca., 95616

Clinically alfentanil (A) has been used effectively for inducing anesthesia and as a supplement to other inhalation drugs; yet its effect on the cardiovascular system remains unclear. Under halothane (H) anesthesia, 8 dogs were instrumented with pressure and ultrasonic dimension transducers to examine regional function and the slope (E_{es}) of the end-systolic pressure-diameter relationship of LV. Cardiac output (CO) was measured by thermodilution and its distribution by radioactive microspheres. A, loading dose (45 µg/kg) followed by an infusion (3 µg/kg/min), produced no change from the control level in segmental length, wall thickness or E_{es} (10.6 ± 1.3 mmHg/mm). While CO did not change significantly from 2.9 ± 0.2 l/min, SAP fell by 18 ± 5% from 85 mmHg. After 10 min of infusion, total vascular resistance decreased by 19 ± 5% but returned to control level (.03 ± .002 mmHg/ml/min) at 15 min. Peak LVP fell from 102.8 ± 2.6 to 88.6 ± 5.2 mmHg without significant change in LV end-diastolic pressure. Blood flow to ventricular septum and freewall did not change; however, it fell by 25 ± 6% from 607 ± 37 ml/min/100g in kidney, and, more remarkably, by 60 ± 6% ($p<.01$) (from 33.8 ± 5.6 ml/min/100g) in liver without significant changes in other organs. Plasma concentration of A rose to and maintained a plateau at 29 ± 5 ng/ml with infusion. Vascular response to A was completely blocked by naloxone. Thus, cardiac contractility and perfusion were well supported after A infusion in a canine model.

7.10

SIMULTANEOUS MEASUREMENT OF VENOUS RETURN AND CARDIAC FUNCTION RELATIONSHIPS. A.S. Greene*, A.A. Shoukas The Johns Hopkins University School of Medicine, Baltimore, MD. 21205

The venous return curve measured with a right heart bypass is commonly used to determine the state of the vasculature. We have used a modified pump bypass to simultaneously measure the right and left heart cardiac function relationships as well as the systemic venous return curves under the influence of the carotid sinus baroreceptors. In ten pentobarbitol anesthetized dogs whose carotid sinus regions had been vascularly isolated a pump was interposed between the great viens and the right atrium. Blood could drain either into a reservoir or directly into the pump. Changes in reservoir volume indicated changes in vascular capacity. Changing carotid sinus pressure from 50-200 mmHg caused a change in reservoir volume of 9.0 ml/Kg. This corresponded to a measured change of 6.2 mmHg in the intercept of the venous return curves. Baroreceptors did not cause a change in the slope of the venous return curves. Changes in cardiac function were only apparent under conditions of constant afterload. We conclude that baroreceptors change cardiac output primarily by a change in vascular capacity.

7.11

COMPARISON OF LEFT VENTRICULAR FUNCTION DURING BLOCKADE BY TWO DIFFERENT β-BLOCKERS: ROLE OF I.S.A. M.L. Smith*, J.V. Nixon, A.W. Jackson and P.B. Raven. Dept of Physiology, Texas College of Osteopathic Medicine, Fort Worth, Texas 76107

A comparison of left ventricular (LV) function between Propranolol (Pr) and Pindolol (Pi) was made on ten healthy males undergoing wide variations in preload. The ten-fold difference in potency of Pi compared to Pr was corrected by dose administered (Pi=0.01 mg/kg and Pr=0.1 mg/kg) thereby enabling evaluation of the intrinsic sympathomimetic activity (ISA) of Pi. M-mode echocardiographs, auscultatory blood pressures and heart rates were determined during increased preload (90 min of 5° head down tilt) and decreased preload (incremental lower body negative pressure to -40 torr). The overall changes in LV function were observed regardless of preload. Selected results of changes from control values are summarized below:

	ΔHR (b/min)	ΔSBP (torr)	ΔVcf (circ/S)	Δcardiac work (%)
Pr	-6.12	-4.6	-0.098	-9.47
Pi	-2.88	-1.95	-0.028	+2.13
P val.	<0.01	<0.01	<0.01	<0.01

In addition, Pr increased End-Diastolic Volume more than Pi ($P<0.01$) without differences in stroke volume or ejection fraction ($P>0.05$). In conclusion, the effect of ISA is to reduce LV wall stress by effecting increases in chronotropy and raising cardiac minute work. However, the LV inotropic depression induced by β-blockers is less for Pi than Pr and may well result from ISA. (Supported in part by a grant from Sandoz Company, Inc.)

8.1

MEAN ALVEOLAR PRESSURES DURING HIGH FREQUENCY OSCILLATIONS. Julian Allen*, Ivan Frantz III and Jeffrey Fredberg. The Children's Hospital, Boston, MA 02115 and The Biomechanics Institute, Boston, MA 02215.

Mean alveolar pressure may exceed mean airway pressure during high frequency oscillations (HFO) (Simon et al, Physiologist, 25:282, 1982). In order to assess the magnitude of this effect and its regional inhomogeneity, we studied 6 excised dog lungs during HFO [frequency (f) 2-32Hz; tidal volume, (Vt) 5-80 ml]. We measured mean pressure at the airway opening ($\bar{P}ao$), at the trachea ($\bar{P}tr$), and at 4 alveolar locations ($\bar{P}alv$), using alveolar capsules (Keefe et al, Fed Proc, 42:763, 1983). $\bar{P}ao$ was measured at the oscillator pump wherein the dynamic head was < 0.2 cm H_2O, and thus represented true transpulmonary pressure (Pl). Pl's studied were 6, 10 and 25 cm H_2O. $\bar{P}alv$ and $\bar{P}ao$ were nearly equal at all Pl, f, and Vt's, except at Pl = 6, f = 32 Hz, and Vt = 80 ml, where ($\bar{P}alv$ - $\bar{P}ao$) was 2.6 cm H_2O. $\bar{P}alv$ and $\bar{P}tr$ were the same at low f and Vt, but $\bar{P}alv$ exceeded $\bar{P}tr$ as f and Vt increased, with ($\bar{P}alv$ - $\bar{P}tr$) approaching 11.5 cm H_2O. Mean pressures in basilar alveoli exceeded those in apical alveoli by up to 3 cm H_2O at high f and Vt. We conclude that global alveolar overdistension is small during HFO under these conditions, but that this fact may conceal significant differences in regional $\bar{P}alv$'s which may be a consequence of differing regional flows (Allen et al, Fed Proc, 43:508, 1984). Most of the differences between $\bar{P}alv$ and $\bar{P}tr$ are related to the dynamic head in the trachea. Support: NIH Grants HL27372, HL26800 and the Parker B. Francis Foundation.

8.2

INHOMOGENEITY OF ALVEOLAR PRESSURES DURING FORCED EXPIRATION IN EXCISED CANINE LUNGS. J.J. McNamara*, R.G. Castile, G.M. Glass*, J. Mead, J.J. Fredberg. Harvard School of Public Health and The Children's Hospital, Boston, MA 02115, and The Biomechanics Institute, Boston, MA 02215.

We investigated the magnitude of and differences in lobar alveolar pressures during forced expirations in five excised canine lungs. Alveolar pressures (P_A's) were measured simultaneously in each of six lobes using an alveolar capsule technique (Fredberg et al., J Appl Physiol, in press) during three quasistatic (QS) deflations lasting > 10 seconds and five forced maximum expiratory dynamic maneuvers. Volume was obtained as the integral of flow from a 19.6 L plethysmograph. Regional lobar P_A's were plotted versus global lung volume. During QS deflations regional P_A's were virtually identical in each dog. During the dynamic deflations regional P_A's diverged markedly especially at lower lung volumes. To quantitate this variability we compared the coefficients of variation of lobar P_A's measured at 75, 50 and 25% of expired vital capacity (VC) during dynamic maneuvers to those during QS maneuvers. Coefficients of variation for the dynamic maneuvers were significantly greater than those for QS maneuvers at all 3 lung volumes ($p < .01$). Thus at a given global lung volume P_A's differ between lobar regions during a maximum expiratory flow maneuver. To the degree that P_A is an index of regional lung volume, our findings imply that the various lobar regions empty inhomogeneously. Supported by NIH Grant Nos. HL27051 and HL07010.

8.3

RATES OF ALVEOLAR PRESSURE CHANGE DURING FORCED EXPIRATION IN CANINE LUNGS. R. Castile, J. McNamara*, G. Glass*, J. Mead and J. Fredberg. Harvard School of Public Health, Biomechanics Institute and Children's Hospital, Boston, MA 02115.

In excised canine lungs, flows during forced expiration are limited by a tracheal choke point over much of the vital capacity. Tracheal choking produces a plateau in flow-volume curve configuration that ends in an abrupt decline in maximal flow which is associated with upstream choke point movement. To assess homogeneity in rates of lung emptying during tracheal flow limitation, we measured, in 5 excised canine lungs, rates of alveolar pressure change ($\dot{P}_A$) simultaneously in each of 6 different lobes using an alveolar capsule technique (Fredberg et al., J Appl Physiol, in press). Global flow ($\dot{V}$) and regional lobar $\dot{P}_A$'s were plotted versus expired volume (V). While global $\dot{V}$ remained unchanged, $\dot{P}_A$'s were not uniform but rather decreased or increased in reproducible lobar patterns. There was consistency to the order in V at which $\dot{P}_A$'s changed, with those showing the largest and most rapid increases occurring near the end of the flow-volume plateau. In all lobes except one, $\dot{P}_A$'s declined before the abrupt fall in global $\dot{V}$. The fall in the last lobe coincided with the drop in global $\dot{V}$. The ordered nature of changes in regional lobar $\dot{P}_A$'s during tracheal flow limitation is consistent with the hypothesis of Mead (Fed Proc 39:2771, 1980) which suggests that upstream choke points may form and influence regional emptying while the downstream tracheal choke persists. Support: NIH Grants Nos. HL27051 and HL07010.

8.4

PARASTERNAL INTERCOSTAL LENGTH RELATED TO RIBCAGE DISPLACEMENT IN DOGS. **André DeTroyer, Michael B. Reid*, and Marc Decramer*. Meakins-Christie Labs., McGill Univ., Montreal H3A 2B4, Que., Canada, and Dept. of Environmental Science and Physiology, Harvard School of Public Health, Boston, Massachusetts 02115, and Chest Service, Erasme University Hospital, 1070 Brussels, Belgium.**

We examined the relationship between parasternal intercostal length (PSL) and rib cage cross-sectional area (Arc) in 9 supine dogs during passive inflation and during quiet breathing before and after phrenicotomy. PSL was measured using a sonomicrometry technique and Arc was estimated with respitrace coils. During passive inflation, PSL decreased as Arc increased. During inspiration in both the intact and phrenicotomized animal, PSL always decreased as Arc increased but the relationship was almost invariably different from that during passive inflation such that the same increase in Arc was associated with a greater decrease in PSL. This difference between passive inflation and active breathing is likely to be due to the fact that the sternum moves cephalad during passive inflation and caudad during active inspiration. In upright man, in view of the fact that the sternum moves cephalad and not caudad, during active inspiration, the relationship between PSL and Arc during active inspiration is most likely to be identical to that during passive inflation. We propose two explanations for the discrepancy between upright man and supine dogs: 1) different properties of the ribcage between the two species and/or, 2) EMG activity in the scalenes present during quiet breathing in man but not in anesthetized dogs. (Supported by MRC of Canada)

8.5

PARASTERNAL INTERCOSTAL LENGTH DURING STATIC AND DYNAMIC RESPIRATORY MANEUVERS. **Marc Decramer* and André De Troyer. Meakins-Christie Labs., McGill Univ., Montreal H3A 2B4, Que. Canada, and Chest Service, Erasme Univ. Hosp. 1070 Brussels, Belgium.**

In order to understand the role of the parasternal intercostals in respiration, we measured the changes in length undergone by these muscles during a variety of static and dynamic respiratory maneuvers. Changes in parasternal intercostal length (PSL) were assessed with pairs of piezo-electric crystals in 39 intercostal spaces from 10 anesthetized dogs. During static maneuvers, the parasternals shortened whenever the rib cage inflated and they lengthened whenever the rib cage contracted. The changes in PSL, however, were small, averaging 9.2% of their FRC length during inflation from RV to TLC and 1.3% during tilting from supine to upright. During quiet breathing, the parasternals always shortened during inspiration. In intact animals, the inspiratory shortening was either greater or close to that seen during passive inflation with the same volume and averaged 3.5%. After bilateral phrenicotomy, however, the decrease in PSL during inspiration markedly increased despite a small decrease in tidal volume. We conclude that: 1) the parasternals in the dog are real agonists (as opposed to fixators) and actively contribute to expand the rib cage and the lung during quiet inspiration; 2) the relationship between lung volume and PSL is not unique but depends on the relative contribution of various inspiratory muscles to tidal volume; and 3) the physiologic range of PSL is considerably smaller than that of the diaphragm. (Supported by MRC of Canada).

8.6

MECHANICAL PROPERTIES AND FATIGABILITY OF NEONATAL BABOON DIAPHRAGM. Roger McCarter, Thomas Kuehl, Charles Compton* and James Robotham. Univ. of Texas Health Science Center, San Antonio, TX 78284.

Fatigue of the diaphragm (DPH) may play a major role in respiratory failure of human infants. We have investigated fatigue of respiratory muscle in neonatal baboons, where the respiratory distress syndrome closely resembles that of humans. Experiments were conducted in vitro using massive direct stimulation of intact muscle, so that complications due to inadequate blood supply or neuromuscular transmission were avoided. Isometric and after-loaded isotonic measurements were conducted at 24C using intact slips of DPH obtained from anesthetized neonatal baboons (Papio cynocephalus, newborn up to 1 month old) and from young adult baboons (8 years old). Contraction and half-relaxation times were significantly longer for neonatal muscles but maximum isometric tension, maximum velocity of shortening and twitch: tetanus ratio were similar for both groups. Neonatal DPH had the same resistance to fatigue as adult DPH but recovered from fatigue more rapidly. Surprisingly, measured mechanical properties were independent of pH and there were only small changes in fatigability in the pH range 6.8-7.4. Work supported by NIH Grant HL2977.

8.7

DECAY OF INSPIRATORY MUSCLE PRESSURE DURING EXPIRATION IN CONSCIOUS MAN. **C.D. Shee*, Y. Ploysongsang*, and J. Milic-Emili. Meakins-Christie Labs., McGill Univ., Montreal, Quebec, Canada.**

Expiration is not a passive process as post-inspiratory inspiratory muscle activity, $P_{mus}I$, causes braking of flow. We have measured $P_{mus}I$ decay during resting breathing in 8 healthy males (age range: 25-35 yrs.). $P_{mus}I$ was calculated by the method of Zin et al (J. Appl. Physiol. 52: 1266-1271, 1982) based on the measurement of changes in lung volume (V) and airflow ($\dot{V}$) during spontaneous expiration, together with measurement of total respiratory system elastance, E_{rs}, and resistance, R_{rs}. E_{rs} was measured by the relaxation method of Rahn and amounted to 8.15±1.35 $cmH_2O.l^{-1}$ (mean±SD). R_{rs} was determined by the interrupter method, the mean value being 2.18±0.34 $cmH_2O.l^{-1}.s$. V and $\dot{V}$ were measured at 0.2 s intervals throughout expiration in 10 breaths per subject. There was an initial fairly rapid $P_{mus}I$ decay followed by a later slower decay. The mean time for $P_{mus}I$ to reduce to 50% and to zero amounted, respectively, to 23% and 79% of expiratory time, T_E. The duration of $P_{mus}I$ was a major determinant of T_E, and, during expiration, 45-76% of the elastic energy stored during inspiration was wasted in terms of negative inspiratory muscle work.

Supported by Medical Research Council of Canada.

8.8

THERAPEUTIC EFFECT OF LATERAL POSTURE IN SLEEP APNEAS. Bashir Chaudhary*, Tesneem Chaudhary*, Ralph Kolbeck and William Speir* Medical College of Georgia, Augusta, Georgia 30912

The effect of the lateral posture on the severity of sleep apneas has not yet been reported. We evaluated 3 patients with obstructive sleep apnea who were able to sleep continuously for prolonged periods of time in one posture. Each patient had two 6-8 hour polysomnographic recordings. The total number of apneas (TA), total sleep time (TST), mean apneic duration (AD), apnea index (AI), apnea/sleep % (A/S) while sleeping on the back (a) and sleeping in the right lateral posture (b) are shown below.

Age/Wt. kg.		TA		TST		AD		AI		A/S	
		(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)
40, 113	A.	174	17	4.10	1.25	28	18	33	14	30	6.8
	B.	30	19	0.95	4.17	21	22	32	5	18	2.8
43, 69		39	0	3.23	2.02	14	0	12	-	4.8	-
68, 105		81	1	3.60	4.90	18	15	22	0.2	11	0.09

The first patient slept in both postures and the remaining two slept in only one posture during the recordings. A beneficial effect of lateral posture was noted in all patients. All had enlarged uvula with no other abnormality of the airway and the beneficial effect may be related to less obstruction of the upper airway from uvula in the lateral position. We conclude that sleeping in the lateral posture appears to have a beneficial effect on the severity of obstructive sleep apneas and this therapeutic maneuver may be used in patients who have enlarged uvula and decline uvulopulatoplasty.

8.9

INCREASED SPECIFIC AIRWAY RESISTANCE (sRaw) IN ASTHMATICS EXERCISING WHILE EXPOSED TO 0.18 PPM OZONE (O_3). D. Horstman, L.J. Roger,* W. McDonnell* and S. Salaam.* U.S. EPA-HERL, Research Triangle Park, NC 27707

Asthmatics have not been shown to be more responsive to O_3 than normal subjects when pulmonary function was evaluated by forced expiratory spirometry. However, sRaw is a more specific and more sensitive indicator of bronchoconstriction, the hallmark of asthma. To evaluate their bronchoconstriction response to O_3, pre and post exposure sRaw and forced expiratory volume in 1 sec (FEV1) were measured for 21 nonsmoking, mild, methacholine sensitive asthmatics (aged 18-35) exposed for 2 hr to 0.00 and 0.18 ppm O_3. Exposure consisted of four sequences of 15 min rest and 15 min moderate exercise ($\dot{V}E$=21 l/m^2 BSA x min) in a chamber at 26°C, 70% RH. When compared with exposure to 0.00 ppm, significant increases in sRaw ($p < 0.01$) and decreases in FEV1 ($p < 0.05$) were observed following exposure to 0.18 ppm O_3 [means (SE)]:

	sRaw ($cm\ H_2O$ x min)		FEV1 (liters)	
	0.00 ppm O_3	0.18 ppm O_3	0.00 ppm O_3	0.18 ppm O_3
Pre	6.52 (0.70)	5.99 (0.50)	3.78 (0.16)	3.79 (0.16)
Post	7.47 (0.76)	9.21 (1.50)	3.76 (0.16)	3.59 (0.18)
Diff	0.95 (0.54)	3.22 (1.38)	-0.02 (0.05)	-0.20 (0.09)

While the decrement in FEV1 is comparable to that reported for normal subjects under similar exposure conditions, the increase in sRaw is greater indicating that our asthmatics were more responsive to O_3 than normals.

8.10

SURFACE TENSION-VOLUME (γ-V) BEHAVIOR OF LUNGS. **J.C. Smith* and D. Stamenovic* (SPON: J. Mead). Respiratory Biology Program, Harvard School of Public Health, Boston, MA 02115.**

Values of alveolar surface tension (γ) have been previously obtained from direct measurements in subpleural alveoli, or estimated from analytical models for lung parenchyma, but γ-V relations over a wide range of inflation-deflation pressure-volume (P-V) histories are still uncertain. We have deduced γ-V relations from measurements of P-V curves of excised, liquid- and air-filled rabbit lungs. P-V curves were obtained at room temperature in (1) lungs filled with test liquids with specific liquid-liquid interfacial tensions with alveolar surface active materials; or (2) air-filled lungs before and after the alveolar surface film was replaced by test liquids with specific values of γ at the air-liquid interface. Values of γ were obtained from points of intersection between P-V curves of normal air-filled lungs and the lungs with test liquids. Interfacial tensions of the test liquids were measured in a surface balance on monolayers of dipalmitoyl phosphatidylcholine. The γ-V relationship in the normal air-filled lung shows a large hysteresis and during deflation from total lung capacity it agrees with the γ-V curve obtained by Schürch (Respir. Physiol. 48, 339-55, 1982). Our results should be useful for testing predictions of P-γ-V relations calculated from recent lung microstructural models, and for comparisons to the behavior of lung surface active materials measured on surface balances. **(Supported by HL 26968 and HL 07118.)**

8.11

A MODELING STUDY OF THE CONSEQUENCES OF CONSTANT FLOW DURING INSPIRATION. **Jason H.T. Bates*, Andrea Rossi* and Joseph Milic-Emili. Meakins-Christie Laboratories, McGill University, Montreal, P.Q. H3A 2B4.**

For a respiratory system with constant compliance and resistance a constant flow can occur during part or all of inspiration in two important situations: when the flow is constrained to be constant throughout inspiration such as is the case with some mechanical ventilators, and when the applied pressure is a ramp (i.e. increasing constantly with time) which may occur during spontaneous breathing. After initial transients in pressure and flow, respectively, have decayed away both situations result in linear volume-time and pressure-time relationships. The slope and intercept of the corresponding pressure-volume line then yields estimates of the effective compliance and resistance, respectively, of the respiratory system. We have shown theoretically that, for a model composed of two compartments in parallel, the effective compliance is the same as the static compliance and equals the sum of the compliances of the two compartments. Furthermore, this compliance is independent of the breathing frequency. However, the effective resistance is, in general, a function of both the individual resistances and the compliances. When the time-constants of the two compartments are equal the effective resistance assumes its minimum value and becomes independent of the compliances. Our model predictions are in accord with data obtained from mechanically ventilated patients. (Supported by MRC, Canada)

8.12

PARTITIONING OF PULMONARY RESISTANCE INTO CENTRAL AND PERIPHERAL COMPONENTS IN HEALTHY SUBJECTS AND PATIENTS WITH CHRONIC PULMONARY EMPHYSEMA. Hirosuke Kobayashi*, Tetsuro Yokoyama, Takeo Kawashiro*, Tadashi Abe*, Makoto Yonemaru*. Dept. of Medicine, Keio Univ., Shinanomachi 35, Shinjukuku, Tokyo 160, Japan.

We partitioned pulmonary resistance into the central and peripheral components non-invasively, irrespective of the chest wall interferances. The subject was oscillated from mouth during normal breathing using summation wave with the frequency over the range of 4Hz to 20Hz. Pleural pressure was measured by an esophageal balloon, in which a catheter-tip micromanometer was installed. Mouth pressure was measured by a pressure transducer, and mouth flow by a pneumotachograph. The outputs of the transducers were taken by a digital computer through band-pass filters. The fast Fourier transformation of the data was performed to obtain the impedance-frequency relationship, from which parameters in a lung model with central airway and peripheral lung components were estimated using a non-linear least square method. In healthy subjects (n=10) the central airway resistance was 0.76 ± 0.65 $cmH_2O/l/sec$ and the peripheral airway resistance was 0.66 ± 0.49 $cmH_2O/l/sec$. On the other hand, in the patients with chronic pulmonary emphysema (n=7) the central airway resistance was 0.50 ± 0.57 $cmH_2O/l/sec$ and the peripheral airway resistance was 6.89 ± 4.59 $cmH_2O/l/sec$.

9.1

MYOCARDIAL FUNCTION AND MORPHOLOGY IN RAT HEARTS PERFUSED WITH KREBS-HENSELEIT SOLUTION AND PERFLUOROCARBON EMULSION. Pasha Rahamathulla*, Kozo Watanabe*, Muhammed Ashraf*, Ronald W. Millard. Univ. of Cincinnati, Cincinnati, OH 45267

The ability of an oxygenated perfluorocarbon (PFC) emulsion to prevent early signs of myocardial cell stress associated with Krebs-Henseleit (K-H) perfusion was evaluated in isolated rat hearts supported in a Langendorff apparatus. Throughout the two-hour perfusion, hearts in both perfusion groups had similar left ventricular pressure and rate of left ventricular pressure development (dP/dt). Coronary perfusate flow was 7.9 ± 0.2 ml/min initially and after two hours of perfusion was 6.6 ± 1.0 ml/min in the K-H group (n=6) and 2.2 ± 0.1 ml/min in the PFC group (n=6). Oxygen content of the perfusate in the two groups was 1.5 ± 0.1 ml/100 ml and 3.4 ± 0.1 ml/100 ml, respectively. Perfusate lactate levels rose from zero to 24 ± 8 µg/ml in the K-H group and to 10 ± 3 µg/ml in the PFC group. Small differences were noted in myocardial cell injury and in total calcium content between the two groups. We conclude that early signs of anerobic metabolism are retarded by perfusion with PFC emulsions and that ventricullar contractile performance is maintained by approximately one-half coronary perfusate flow in the PFC hearts. The mechanism whereby coronary flow is regulated downward in the PFC perfused hearts remains unanswered.

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9.2

CATALYTIC AND STRUCTURAL STABILITY OF PHOSPHOFRUCTOKINASE FROM RAT MYOCARDIUM AS A FUNCTION OF pH, METABOLITES AND ORGANIC SOLUTES IN VITRO. Steven C. Hand and John F. Carpenter*. University of Louisiana, Lafayette, LA 70504

Phosphofructokinase (PFK) isolated from the rat myocardium to a purity of greater than 95% is inactivated under a pH regime approximating that reported for ischemic hearts. At pH 6.5 and 37°C, the enzyme displays a time-dependent loss of activity during 60-minute incubations, declining to 48% of control (pH 7.1, 37°C) values. Citric acid (0.5-2 mM) accentuates the inactivation (28% of control), while positive modulators like fructose 1,6-bisphosphate reduce the decline in activity. Physical measurements of the purified enzyme, including light scattering and enhancement of fluoresence using the extrinsic probe 2-(N-methylanilino)naphthalene 6-sulphonate, suggest the inactivation results from dissociation of the active tetrameric enzyme into inactive dimers. Reactivation of the dimerized PFK occurs upon returning the enzyme to control pH values. The rate of reactivation is not only dependent on PFK concentration, but is markedly increased in the presence of trimethylamine N-oxide, a naturally-occurring osmolyte noted for its ability to promote protein aggregation reactions. These in vitro results suggest that the influence of pH on the tetramer-dimer equilibrium could explain in part the glycolytic inhibition observed during ischemia in the rat heart. (Supported by the American Heart Association-LA, Inc. and NSF Grant PCM-8316711)

9.3

CARBOHYDRATE METABOLISM DURING HYPOTHERMIC CARDIOPLEGIA

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Under hypothermic cardioplegia, the energy supply to the heart muscle changes from oxidative phosphorylation to anaerobic glycolysis after rapid depletion of myocardial oxygen reserves. The understanding of carbohydrate metabolism during hypothermic elective cardiac arrest may provide useful information to improve myocardial preservation during cardiac surgery. Isolated perfused working rat hearts under simulated surgical conditions were used for this study. A significant decrease in creatine phosphate was observed within 5 min after the initiation of cardioplegia, and decreased to a very low level at 30 minutes of ischemic period. Significant amounts of lactate began to accumulate 10 min after elective cardiac arrest, and increased to more than 5.5 times the original amount at the end of the ischemic interval. No significant changes in glucose -6-phosphate (G-6-P) and ATP levels were observed during the first 10 min. of ischemic arrest. A progressive decrease of ATP occurred during the first 30 min of arrest and maintained at this level during the remainder of the arresting period. The G-6-P accumulation reached significant levels at 30 min and peaked at the end of 60 min of ischemia. From the time dependent changes in myocardial high-energy phosphates, glucose and glycogen, and the intermediate metabolites we concluded that during hypothermic cardioplegia the G-6-P accumulation was due to the breakdown of glycogen and the inhibition of its utilization. Supp. by NIH grant HL-32231.

9.4

REVERSIBLE INACTIVATION OF PHOSPHOFRUCTOKINASE DURING ISCHEMIA IN THE PERFUSED RAT HEART. John F. Carpenter* and Steven C. Hand. University of Louisiana, Lafayette, LA 70504

Under acidotic conditions in vitro, tetrameric phosphofructokinase (PFK) dissociates into inactive dimers. To determine if this shift in the tetramer-dimer equilibrium is operative in vivo in the ischemic rat heart, we have prepared antiserum against purified rat heart PFK and developed a rocket immunoelectrophoresis (IE) assay to quantify these two molecular species. IE of purified PFK incubated under conditions promoting a stable tetramer results in rockets which can be stained for PFK activity. Incubation under conditions known to induce dimerization does not. With protein staining, both the tetramer and dimer rockets can be visualized in the same sample. PFK activity in homogenates of Langendorff perfused hearts decreases with increased duration of global ischemia. After 40 min. of ischemia, PFK activity is reduced to 50% of that for control normoxic hearts. Incubation of the supernatants at 37°C for 1 hr. results in a 30% activation of PFK from ischemic hearts. Results from IE demonstrate that inactivation during ischemia correlates with a shift in the tetramer-dimer equilibrium toward dimers and that the converse is true for reactivation. These findings indicate that PFK may be regulated in vivo by alterations in tetramer-dimer equilibrium. (Supported by the American Heart Association-LA, Inc. and NSF Grant PCM 8316711).

BLOOD PRESSURE CONTROL

10.1

PARASYMPATHETIC RESPONSE TO INTRACAROTID (IC) PROSTAGLANDIN E_2 (PGE_2) IN CONSCIOUS SHEEP. B.A. Breuhaus* and J.E. Chimoskey, Michigan State University, East Lansing, MI 48824.

Infusion of PGE_2 10 ng/kg/min IC in 8 conscious sheep increased blood pressure (BP) 22 mmHg and heart rate (HR) 14 bpm ($p<.05$). Atropine methyl bromide (A), 1 mg/kg intravenously (IV), increased BP 8 mmHg 5 minutes (min) and 4 mmHg 30 min after administration ($p<.05$). When A was given before or during PGE_2 the BP response equalled the response to PGE_2 alone. HR increased 22 bpm 5 min and 24 bpm 30 min after A ($p<.05$). When A was given before or during IC PGE_2 the HR response equalled the sum of the HR responses to each drug separately. Propranolol (P), 1 mg/kg + .025 mg/kg/min IV, did not change BP or HR. When P was given before or during IC PGE_2 the BP response equalled the response to PGE_2 alone. HR increased during PGE_2 plus P, but was less than HR during PGE_2 alone. When all 3 drugs were given together, BP equalled BP during PGE_2 alone. This BP increase was less than the sum of the BP increases during administration of each drug separately ($p<.05$). The HR increase when all 3 drugs were given together was the same as during A alone. This HR increase was less than the sum of the HR increases during administration of each drug separately ($p<.05$). When PGE_2 was given during A, HR increased as much as during PGE_2 alone due to greater ß-adrenergic activation. Inhibition of resting parasympathetic tone by IC PGE_2 became manifest only during ß-adrenoceptor blockade. Michigan Heart Assoc., NIH HL07404, HL06840, HL30239.

10.2

BLOOD PRESSURE AND VASOPRESSIN RESPONSES TO CHANGES IN BLOOD VOLUME IN ANAESTHETIZED RABBITS. C.A. Courneya*, J.R. Ledsome, N. Wilson*, A.J. Rankin*. Department of Physiology, University of British Columbia, Canada, V6T 1W5

Plasma vasopressin (AVP) is known to be influenced by changes in blood volume. Atrial receptors and arterial baroreceptors contribute to the response. Few measurements have been reported of changes in plasma AVP in rabbits in response to stimulation of vascular receptors. In anaesthetized rabbits (pentobarbitone-urethane) measurements were made of right atrial pressure (RAP), left atrial pressure (LAP) through a midline thoracotomy, femoral arterial pressure (FAP) and plasma AVP (by radioimmunoassay). Blood volume was altered by stepwise haemorrhage and infusions of whole blood from a donor rabbit. Recording and sampling of blood was carried out 5 min after each change in blood volume. Haemorrhage of 3 ml/kg decreased FAP 13%, RAP 20%, LAP 23% and increased plasma AVP 16%. Volume expansion of 8 ml/kg increased FAP 14%, RAP 19%, LAP 25% and decreased plasma AVP 17%. The pattern of change in LAP was similar to the change in RAP. Thus measurements of RAP indicate changes in both RAP and LAP under these conditions. Plasma AVP changes in response to step changes in blood volume in the rabbit. The relative importance of changes in RAP or FAP in inducing changes in plasma AVP cannot be determined from these data. (Supported by grants from MRC, B.C. Heart Foundation and BCHCRF.)

10.3

INFLUENCE OF VASOPRESSIN (VP) ON CARDIAC OUTPUT (CO) AND BLOOD PRESSURE (BP) DURING HEMORRHAGE IN CONSCIOUS RATS. D.E. Allen and B.R. Edwards. Dartmouth Medical Sch., Hanover, NH 03756

We examined VP's role in compensating for hemorrhage in chronically instrumented rats, free from effects of anesthesia and surgery on BP control systems. 13 males (BW 324±7g) were implanted with ascending aortic pulsed Doppler flow probes for CO monitoring and femoral arterial and venous catheters, then allowed 7 days recovery. Hemodynamic (HD) variables were recorded during a control (C) period, throughout 2 hemorrhages (H1-1.3%BW; H2-.5%BW) and after blood return. Plasma renin activity (PRA) was measured in C and during H1. Each rat was studied on 2 separate days: in the absence (noPA) or presence (PA rats) of a VP pressor antagonist (10µg/kg + 5µg/kg/hr). C values of all variables did not differ in noPA or PA rats. 5 min after H1 onset, mean arterial pressure (MAP) dropped to 63 ±6.4mmHg in PA rats, and to 77±3.5 in noPA rats. At no further point in H1 was MAP significantly higher in PA rats (30 min values: 93±1.5 noPA vs 89±4.5 PA). CO fell from 7.6±0.3 to 5 ±0.4 (PA) and from 7.6±0.2 to 5.1±0.3 kHz shift (noPA) at H1 onset, never varying significantly between PA and noPA during H1. TPR was slightly elevated throughout H1 in noPA rats; in PA rats, TPR initially fell, rising to the C value (14±0.6) by 20 min of H1. PRA at end H1 had not been increased by VP block. We conclude that while the CV action of VP does influence the HD response to hemorrhage in conscious rats, it does not confer a better compensatory ability.

10.4

EFFECT OF VASOPRESSIN BLOCKADE ON BLOOD PRESSURE IN EUHYDRATED AND DEHYDRATED BABOONS. K.L. Ryan*, R.M. Thornton and D.W. Proppe. Univ. of Texas Hlth. Sci. Ctr., San Antonio, TX 78284.

The objective of this study was to determine the role of vasopressin (VP) in the maintenance of arterial blood pressure (ABP) in unanesthetized, chronically instrumented baboons in both euhydrated and dehydrated states. Dehydration was produced by 68-72 hours of fluid deprivation. In four baboons, VP blockade (VPB) was induced in the presence and absence of a functioning renin-angiotensin system (RAS) by the VP antagonist TMe-AVP (10µg/kg, IV). RAS blockade was induced by captopril. Dehydration produced statistically significant ($p<.05$) increases in plasma osmolality (290±1(SE) to 326±4 mOsm/kg), sodium (143±1 to 160±2 mEq/L), and total proteins (6.89±0.20 to 7.96±0.19 g%). In the presence of a functioning RAS, VPB produced no change in ABP in either euhydrated (82±4 to 80±3 mmHg) or dehydrated (99±4 to 94±4 mmHg) states. Likewise, VPB resulted in no changes in heart rate (HR) in either euhydrated (88±10 to 92±13 bpm) or dehydrated (132±17 to 145±19 bpm) states. During RAS blockade, VPB again produced no change in ABP in either euhydrated (77±2 to 79±5 mmHg) or dehydrated (83±1 to 77±1 mmHg) states. During RAS blockade, VPB did produce a rise in HR in euhydrated (100±4 to 117±12 bpm) and dehydrated (138±16 to 161±17 bpm) states, but this rise in HR occurred only at 25 minutes after induction of VPB. These results suggest that VP has a minor role in the maintenance of ABP in baboons in both euhydrated and dehydrated states. (Supported by HL 27504).

10.5

BLOOD PRESSURE REGULATION IN CARDIAC DENERVATED DOGS DURING LOW-FREQUENCY SINUSOIDAL ACCELERATION, C.F. Knapp*, J.M. Evans*, & D.C. Randall. Univ. Kentucky, Lexington, KY 40506.

Previous experiments (Am.J.Physiol. 243: H998, 1982) showed that dogs with intact cardiac nerves minimized arterial pressure fluctuations(ΔAP) induced by ±2Gz sinusoidal acceleration from .005 to .032 Hz when compared to the pharmacologically blocked (B) state (propranolol, phentolamine, atropine). Here, we compare ΔAP in cardiac denervated (D) vs intact (I) dogs to determine the role of the cardiac afferent and efferent nerves in pressure homeostasis. The chronically instrumented dogs (n=5) were sedated (Innovar-Vet) during the centrifugation protocol. Experiments were conducted with and without B. The unblocked D dogs experienced significantly larger (35 to 70%) gravitationally-induced ΔAP over the lower frequency range (to .077 Hz) than I dogs. Peak values of ΔAP occurred between .032 -.052 Hz for both groups, reaching 78 mmHg for D dogs and 45 mmHg for I dogs. There were no differences between D and I animals between .077 and .025 Hz. ΔAP was similar in both groups for all frequencies following B. Blockade and denervation eliminated acceleration-induced reflex fluctuations in HR. Compensatory changes in total peripheral resistance (TPR) were significantly smaller in D vs I dogs for the lowest frequency range (<.012 Hz). The larger ΔAP in D animals appears to be due to 1) diminished HR and TPR response, and/or 2) inappropriate phase relationships with respect to acceleration input, and/or 3) loss of cardiac afferent nerves influencing TPR. (Supported by AFOSR 80-0039 and HL 19343).

10.6

EFFECT OF MARIJUANA (M) AND Δ-9-TETRAHYDROCANNABINOL (THC) ON HEART RATE, BLOOD PRESSURE, AND RESPIRATION IN SHEEP. K. Niederreither* and R. Abrams, Depts. of Physiol. and Ob-Gyn, Univ. of Florida Med. Ctr., Gainesville, FL 32610.

Four nonpregnant ewes were instrumented with tracheal T tubes and femoral artery and vein catheters. Several days post op, one M cigarette containing 3.19% THC was smoked continuously for 10 min in a hand-held smoking machine. Air flow rate was 150 ml/min. Smoke diluted with air from upper airway was introduced to the lower airway through the open-ended T tube. Virtually all mainstream smoke was delivered without significant overt disturbance of the ewe. In other experiments, THC (5 mg in 3 ml absolute ethanol) was infused over 10 min. Behavioral effects noticed after M and THC, but absent after smoking M placebo cigarettes and injection of ethanol vehicle, were marked drooping of the head, spreading of hind legs, and startles. Slight, yet significant reductions in heart rate of 7-15/min were produced by THC but not M or control substances. No effect on blood pressure was noted with either drug or control. M and THC caused dramatic reductions in respiratory rate (typically slowed to 1/4 control values) and increases in depth of breathing which continued for 2 or more hours. (M and M placebo cigarettes and Δ-9-THC supplied by National Institute on Drug Abuse).

CARDIAC ELECTROPHYSIOLOGY

11.1

ELECTROPHYSIOLOGICAL ACTIONS OF DIACETYL MONOXIME, (DAM) IN 3-DAY-OLD EMBRYONIC CHICK HEARTS. **Hideaki Sada* and Nick Sperelakis. Univ. of Cincinnati., Cincinnati, OH 45267**

DAM is a negative inotropic agent (Wiggins et al., 1980, J. Pharm. Exp. Ther., 212:217) and has been shown to uncouple contraction from slow action potentials (Li, Sperelakis, Pan and Solaro, 1984, Fed. Proc., 43:2826). We studied the electrophysiological actions of DAM in 3-day-old embyronic chick hearts, in which the rising phase of the action potentials depends on slow Na^+ channels (Sperelakis and Shigenobu, 1972, J. Gen. Physiol., 60:430). The experiments were carried out in Tyrode solution with $[Ca]_o$ reduced to 0.6 mM (35°C). The effects of DAM (10 mM) on the transmembrane potential parameters, after 10 min exposure, were as follows (expressed as percent change from control, n = 4-10):

	Control	DAM 10 mM (10 min)
HR	1.4 ± 0.1 sec^{-1}	+48 ± 10.8%
V_{max}	15 ± 1.5 V/sec	-45 ± 16.1%
AP/amp	68 ± 4.6 mV	-21 ± 6.6%
MDP	54 ± 3.6 mV	-7 ± 10%
APD_{50}	129 ± 18 msec	-68 ± 2.4%

(HR = heart rate, $\dot{V}_{max}$ = maximum upstroke velocity, AP/amp = action potential amplitude, MDP = maximum diastolic potential, APD_{50} = AP duration at 50% repolarization). Contractions were visibly diminished concomitant with these electrical charges. It is concluded that DAM (10 mM) suppresses the slow Na^+ current and slow Na^+ channels found in 3-day-old embryonic chick hearts. Supported by NIH Grant HL-18711.

11.2

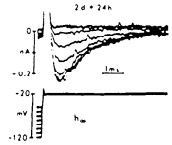
ELECTROPHYSIOLOGY OF ATRIAL PACEMAKERS IN THE EUSTACHIAN RIDGE OF THE CAT HEART. Don Rubenstein* and Stephen Lipsius. Dept. of Physiology, Loyola University Med. Ctr., Maywood, IL

Intracellular recordings were used to study the electrical properties of right atrial pacemakers in the Eustachian ridge of the posterior internodal pathway. Initially, most preparations beat spontaneously without norepinephrine (NE). When quiescent the resting membrane potential (RMP) was relatively positive (-64±2mV). NE (10^{-9}M) or low K_o (1mM) depolarized the RMP causing oscillatory prepotentials and initiation of pacemaker activity (PA). Atenolol blocked NE-induced PA. Pacemaker action potentials had a relatively positive maximum diastolic potential (MDP) (-75±4mV), slow upstroke (7.5±1.2V/sec) and steep phase 4. PA persisted in K_o up to 16 mM. Cesium (Cs;2.5-20 mM) did not abolish PA but depolarized MDP. Low Cs (2.5,5 mM) slightly decreased and high Cs (20 mM) significantly increased PA. Acetylcholine (10^{-7}M) and verapamil completely suppressed PA. Log K_o vs RMP showed a 58 mV/10 fold change and an extrapolated intracellular K concentration of about 155 mM. The calculated P_{Na}/P_K ratio was 0.07. We conclude that slow response pacemakers are present in the Eustachian ridge. NE initiates pacemaker activity via beta-1 receptor activation. The relatively positive RMP is due to a high P_{Na}/P_K ratio and not low intracellular K. These pacemakers are relatively resistant to high potassium and do not depend on a cesium sensitive pacemaker current for automaticity. (Supported by NIH Grant HL27652)

11.3

A FAST INWARD CURRENT IN CELLS ISOLATED FROM 2-DAY EMBRYO CHICK VENTRICLE. S. Fujii, R. K. Ayer,Jr., and R. L. DeHaan, Emory University Medical Center, Atlanta, Georgia 30322

Voltage command (V_{com}) steps (-70 to +80 mV) were applied to single 12-14 um embryonic chick ventricle cells or small cell clusters, with patch electrodes in the whole-cell clamp configuration. Cells isolated from embryos incubated 2, 3, 4, or 7 d were maintained in culture medium for 5-8 h or 24 h after dissociation in 10^{-5}M Ca buffer, with or without trypsin. The time to peak (T_p) and peak amplitude (I_{Nap}) of the initial inward current were measured at 23°C from a constant holding potential (V_H=-80 mV). The h-inactivation relation was determined with steps from V_H of -50 mV to -130 mV, to V_{com}=-20 mV (Fig). Cells from all stages exhibited a fast inward sodium current (I_{Na}) that was suppressed by TTX or low-Na solution. The h-inactivation variable equalled 1 at -130mV and zero at -50mV. After 5-8h of culture, the mean values of I_{Nap} (V_H=-120 mV) and T_p for non-trypsinized 2d cells were 25.0 uA/cm^2 and 1.9 ms; for trypsinized 3, 4 and 7d cells they were 68.4, 31.8 and 239.3 uA/cm^2, and 1.5, 1.2 and 0.8 ms. These values 24h after trypsinization, from 2, 3, 4, and 7d cells were, respectively: 46.9, 98.7, 85.5 and 315.0 uA/cm^2; T_p was: 0.8, 1.0, 0.9 and 0.7 ms. We conclude that functional I_{Na} channels are present in the ventricle after 2 d of incubation (stage 12-13), and that channel density increases with further development. (Supported by NIH PO1-HL27385).



11.4

INTERACTION BETWEEN ISOPROTERENOL, EPINEPHRINE, AND PHENYLEPHRINE WITH INHALATIONAL ANESTHETICS - HALOTHANE, ISOFLURANE, AND ENFLURANE IN THE GUINEA PIG SINO-ATRIAL NODE. Z. Dujic*, Z.J. Bosnjak, and J.P. Kampine. Depts. of Anesth. Physiol., Med. Coll. of Wisconsin and Wood VAMC, Milwaukee, WI 53193.

We examined effects of different inhalational anesthetics and sympathomimetics on the guinea pig SA-node. Spontaneously beating SA-nodes of 50 adult guinea pigs were superfused with Krebs solution. Standard micro-electrode technique was used to measure intracellular action potentials. Between sympathomimetics the order of maximum dose-response was isoproterenol > epinephrine > phenylephine. Included is a Table with the maximal effects of isoproterenol (ISO) on the heart rate (BPM) in the presence of three anesthetics (1 and 2 MAC).

	C	+ISO	1 MAC+ISO	2 MAC+ISO
ENFLURANE	248	366	341	315
ISOFLURANE	286	410	376	338
HALOTHANE	270	383	350	327

In the case of isoproterenol, the order of maximal depression of the maximum dose-response with 2 MAC was isoflurane > halothane > enflurane. Similar tables were obtained with phenylephrine and epinephrine, and the order of maximal depression was halothane > isoflurane > enflurane. (Supp. by NIH GM 29641 and the VA).

11.5

ACTIONS OF BAY K 8644, A NEW "Ca^{2+} AGONIST", ON SLOW Na^+-DEPENDENT ACTION POTENTIALS IN 3-DAY-OLD EMBRYONIC CHICK HEARTS. Nick Sperelakis and Hideaki Sada* University of Cincinnati, Cincinnati, OH 45267-0576

We recently reported that BAY K 8644, a dihydropyridine analog of nifedipine, stimulated/activated the slow Ca^{2+} channels in cardiac muscle (Wahler and Sperelakis, Am. J. Physiol., in press). Young (2-3-day-old) embryonic chick hearts possess spontaneous slow action potentials that are Na^+-dependent (Sperelakis and Pappano, 1969, J. Gen. Physiol., 53:79). Therefore, we studied the actions of BAY K 8644 (10^{-6}M) on the slow Na^+ channels found in 3-day-old embryonic chick heart. The values of the electrophysiological parameters obtained in control medium ($[K]_o$ = 4 mM, $[Ca]_o$ = 0.6 mM; 35°C), and after drug addition were as follows (n = 6-11):

	Control	Change from Control 6-10 min	11-20 min
HR	2.1 ± 0.2 sec^{-1}	+24 ± 9.2%	+37 ± 8.7%
Vmax	20.0 ± 3.8 V/sec	+44 ± 18%	+36 ± 9.7%
AP ampl.	63.8 ± 5.6 mV	+23 ± 7.4%	+11 ± 12%
MDP	51.3 ± 4.4 mV	+14 ± 6%	+ 6 ± 7%
APD_{50}	92.3 ± 19.9 msec	+57 ± 23%	+68 ± 20%

In addition, the drug enhanced the force of contraction. The drug-induced changes in electrical and mechanical activities were reversed only slightly upon washout for 30 min. It is concluded that BAY K 8644 increases the slow Na^+ current. Therefore, this drug appears to activate not only the slow Ca^{2+} channel, but also the slow Na^+ channel found in 3-day-old embryonic chick hearts. (Supported by NIH grant HL-18711).

11.6

REVERSAL OF DIGITALIS-INDUCED VENTRICULAR ARRHYTHMIAS BY VERAPAMIL. E. M. Ballard*, R. J. Armitage*, C. J. Breen*, C. A. Meyer*, M. Babich* & K. C. LEE* (SPON: D. C. Randall). Dept. of Physiol. and Biophy., Uni. of Ky, Lex. KY 40536

Pretreatment with verapamil (Ver) was shown to decrease susceptibility to digitalis-induced ventricular ectopy (FESEB 67:964, 1984). We investigated if digitalis-induced premature ventricular contraction (PVC) and ventricular tachycardia (VT) can be reversed by Ver injection. Five experiments were performed in 3 chronically instrumented, sedated (Innovar-Vet , 0.5-1.0cc) adult dogs. Blood pressure, left ventricular pressure (LVP), d(LVP)/dt, heart rate, and left ventricular myocardial shortening were measured. Drugs were administered into the pulmonary artery. Acetyl strophanthidium (AS), a short acting digitalis, was infused (.5 ml/min, .5 mg/ml) until PVC (AV dissociation, bizarre QRS morphology & weak contractility, 45±10 µg/kg) or VT (AV dissociation, bizarre QRS morphology & tachycardia, 125±25 µg/kg) were observed; Ver (.15 mg/kg) or saline was then injected. PVC lasted 7 min after AS infusion in 1 dog but after Ver injection it could not be observed in another dog. VT lasted ~5 min after AS infusion in 2 dogs, the ventricle then developed fibrillation in 1 dog and asystole in another. In a third dog, Ver injection did not suppress VT, but neither fibrillation nor asystole developed. The results suggested that Ver may reverse digitalis-induced PVC and although VT was not suppressed, it may prevent further cardiotoxicity. (Grant HL-19343)

11.7

DEPRESSION OF MYOCARDIAL SLOW ACTION POTENTIALS (APs) AND CONTRACTIONS BY CYCLIC GMP (cGMP). Gordon M. Wahler and Nick Sperelakis. Dept. of Physiology and Biophysics, Univ. of Cincinnati College of Medicine, Cincinnati, OH 45267.

Our laboratory has shown that intracellular injection of cAMP transiently enhances slow APs in myocardial cells, presumably by phosphorylating slow channels. To test if cGMP also plays a role in cardiac slow channel function, 8-Br-cGMP superfusion or intracellular injections of cGMP were carried out in guinea pig papillary muscles (stimulated at 0.5 Hz at 37° C). The cells were depolarized to about -40 mV with 25 mM K^+-Tyrode's solution to voltage-inactivate the fast Na^+ channels. Slow APs were elicited by electrical stimulation following the addition of 10 mM TEA and doubling bath [Ca] (to 4.0 mM), or by 2 x 10^{-7} M isoproterenol. Slow APs are dependent on the slow inward current (I_{si}) carried through the voltage - and time-dependent slow channels. 8-Br-cGMP (10^{-6} - 10^{-3} M) superfusion depressed or abolished slow APs and accompanying contractions over a similar time course. cGMP (5-100 mM Na^+ salt in 0.2 M KCl) was injected by application of a pressure pulse (40-75 psi, 1-30 sec duration) to the recording microelectrode. cGMP injection resulted in transient depression (n=15) or abolition (n=4) of the slow APs. The effect began 1 min after the onset of the pulse, reached a maximum at 2 min, and recovered fully within 6 min. Thus, the intracellular cGMP level appears to be able to modulate I_{si} (and contractility) in a direction opposite to that of cAMP. This effect may be mediated by phosphorylation of some unknown protein.
(Supported by N.I.H. grant HL-31942 and fellowship HL-06736-01).

11.8

EFFECT OF LOWERING $[Na^+]_o$ ON CARDIAC SLOW ACTION POTENTIALS. Tung Li* and Nick Sperelakis. Dept. Physiology, Univ. Cincinnati, Cincinnati, OH 45267-0576

Lowering $[Na]_o$ depressed and eventually blocked (≤30 mM) cardiac slow action potentials (APs) (Schneider and Sperelakis, 1975, J. Mol. Cell. Cardiol. 7:249). It was proposed that the slow AP might have a significant proportion of the slow inward current (I_{si}) carried by Na^+ or there might be separate slow Na^+ and Ca^{++} channels. Alternatively, low $[Na^+]_o$ could increase $[Ca^{++}]_i$ (by altering Na-Ca exchange rate) leading to an inhibition of the I_{si}. To test this latter hypothesis, procedures were employed to minimize the increase of $[Ca^{++}]_i$ when $[Na^+]_o$ was lowered. Slow APs were induced in guinea pig papillary muscle by 10^{-7}M isoproterenol (ISO) or $BaCl_2$ in Tyrode's solution containing 22 mM KCl. The following results were observed: (1) The time course of the decrease in V_{max} of the ISO-induced slow AP was similar upon superfusion with a low $[Ca^{++}]_o$ solution containing Na^+ with normal or various lowered concentrations. (2) Substituting 1/2 normal $[Ca^{++}]_o$ with Ba^{++}, the slow AP was induced (without ISO) and persisted (without decrease in V_{max}) in low $[Na^+]_o$. (3) The effects of intracellular iontophoresis of EGTA in muscles which had shown contracture and depressed slow APs in low Na^+ and ISO solutions were varied. Frequently, increases in V_{max} and AP duration were observed. It is concluded that an increased $[Ca^{++}]_i$ can be at least partially responsible for the low $[Na^+]_o$ induced depression of cardiac slow channels. Supported by NIH Grant HL-18711.

11.9

EFFECTS OF HIGH K+, ACIDOSIS, HYPOXIA AND GLUCOSE LACK ON INTERNAL LONGITUDINAL RESISTANCE IN VENTRICULAR MUSCLE.
Takao Fujino*, Jack W. Buchanan, Jr.* and Leonard S. Gettes
University of North Carolina, Chapel Hill, NC 27514

Changes in internal longitudinal resistance (r_i) influence the speed of impulse propagation in the heart, particularly if the changes are concentrated at cellular junctions. In guinea pig papillary muscles (N=5), we have investigated the effects on total r_i of simulated ischemia (pH 6.0, K+ 13.0mM, pO_2 20-25 and absent glucose), and have studied the effects of verapamil (10^{-5}M) on this change. r_i was determined by the ratio of intra-to extracellular potentials (V_I/V_O), using an air insulation modification of Weidmann's silicon oil method. Under simulated ischemic conditions, r_i increased and reached twice control (207+/-32SD % control) within 20 minutes. Verapamil slowed the time course of this increase in r_i (153 +/-48SD % control at 20 minutes), although it eventually did not prevent the increase. Using a paired t-test, this difference was found to be significant at the p=.02 level. We conclude that this technique may simulate the ischemic change in r_i occuring in the whole heart and that verapamil may slow this change. We further conclude that the observed changes in r_i may be of sufficient magnitude to significantly influence myocardial conduction, particularly if these changes are concentrated at the intercalated disc region.
Supported by Program Project Grant HL274430 from NHLBI

CONTROL OF BREATHING I

12.1

NALOXONE AND THE CONTROL OF BREATHING IN SUPINE LOW-LEVEL EXERCISE.
D.M. Mathews,* C. Weissman,* J. Askanazi, J.M. Kinney. Departments of Anesthesiology, Surgery and Medicine, Columbia-Presbyterian Hospital, New York, NY 10032.

The role of endogenous opiates in the control of respiration during exercise was studied using a naloxone (NLX) infusion. Six male subjects (age 21-29) were studied at rest and during low-level supine exercise (2.5 and 5.0 kg m/sec) using a non-invasive canopy system. On consecutive days the subjects received either placebo or a bolus infusion of 0.15 mg/kg NLX followed by a constant infusion of 0.15 mg/kg/hr NLX. Mean ± SD:

PLACEBO	$\dot{V}_E$ (l)	V_T (ml)	f (min)	$\dot{V}O_2$ (ml/min)	$\dot{V}CO_2$ (ml/min)	T_I (sec)	T_E (sec)
Rest	5.3	365	15.6	275	211	1.53	2.61
	±.49	±85	±1.7	±27	±30	±.35	±.39
2.5	10.8	582	19.6	515	378	1.40	1.83
	±1.1	±101	±2.0	±31	±50	±.21	±.22
5.0	18.2	877	22.4	846	613	1.29	1.60
	±1.9	±194	±3.5	±37	±18	±.19	±.36
NALOXONE							
Rest	5.0	348	16.1	278	203	1.40	2.49
	±.89	±61	±1.8	±28	±27	±.20	±.38
2.5	10.5	522	20.6	504	361	1.29	1.70
	±1.0	±66	±2.2	±28	±29	±.18	±.19
5.0	16.6	810	21.2	812	575	1.33	1.69
	±2.5	±120	±4.7	±32	±18	±.30	±.42

There is no significant change in respiratory parameters with NLX infusion during rest or low-level exercise.

12.2

SOME CHARACTERISTICS OF A STEADY STATE MODEL OF EXERCISE HYPERPNEA.
W.E. Fordyce and F.M. Bennett. SUNY- Upstate Medical Center, Syracuse, NY 13210 and Dartmouth Medical School, Hanover, NH 03756.

A simple mathematical model of the respiratory control system has been studied to infer some of it's operating characteristics during exercise, CO2 inhalation, and IV CO2 administration. The model is a closed-loop regulator for $PaCO_2$ with a gas exchanger and ventilatory controller incorporating a feed-forward 'exercise factor' proportional to $\dot{V}O_2$ (Grodins, Physiol. Rev. 30:220, 1950). Ventilation is the controlling variable and $PaCO_2$ is the controlled variable. We restrict the model to normoxia and normal acid-base state. A key feature of this model is that it responds to either IV or inhaled CO2 with hypercapnic hyperpnea. Analysis of the model indicates that the open-loop CO2 gain (i.e., $\partial\dot{V}_E/\partial PaCO_2$ (controller) times $\partial PaCO_2/\partial\dot{V}_E$ (gas exchanger)) decreases monotonically with increasing $\dot{V}O_2$ or with decreasing $PaCO_2$ set point. As a consequence, the closed-loop system sensitivity of $PaCO_2$ to $PICO_2$ is increased by exercise or by decreased set point. Also, the system sensitivity of $PaCO_2$ to IV CO2 is decreased by exercise but increased by reduced set point. And a decreased $PaCO_2$ set point increases the closed-loop system sensitivity of $\dot{V}_E$ to $\dot{V}O_2$ even though the controller CO2 and exercise gains remain unchanged. Thus, from the viewpoint of $PaCO_2$ homeostasis, this system has some surprising properties which appear advantageous. (Supported in part by HL-30653).

12.3

GOOD REGULATION OF $PaCO_2$ DURING EXERCISE DOES NOT NECESSARILY IMPLY PRECISE COUPLING BETWEEN $\dot{V}_E$ AND METABOLIC RATE.
F.M. Bennett and W.E. Fordyce. Dartmouth Medical School, Hanover, NH 03756 and SUNY Upstate Medical Center, Syracuse, NY 13210.

Simple mathematical models were used to quantitatively examine a number of hypotheses concerning the nature of the ventilatory exercise stimulus. The modelling demonstrated the following for an exercise intensity of 5X rest. 1)During the steady-state, a deviation in the coupling between $\dot{V}_E$ and $\dot{V}CO_2$ by ± 25% of the value necessary for isocapnia results in a deviation of $PaCO_2$ of ± 2 torr from isocapnia. 2)In the transient phase, a mismatch between $\dot{V}_E$ and Q (and thus CO_2 flow) of ± 50% results in a change in $PaCO_2$ of only ± 1 torr. 3)When resting $PaCO_2$ is changed by ± 10 torr and it is assumed that the coupling between $\dot{V}_E$ and $\dot{V}CO_2$ does not change, $PaCO_2$ deviates from isocapnia by less than 2 torr. It is concluded that 1)to experimentally test hypotheses of the exercise stimulus requires resolution of small differences in $PaCO_2$ of usually less than 2 torr, sometimes less than 1 torr. 2)Good regulation of $PaCO_2$ does not necessarily imply precise coupling between $\dot{V}_E$ & $\dot{V}CO_2$. 3)The ventilatory exercise stimulus need not be a precise function of metabolic rate. 4)In the steady-state, the normal CO_2 controller will be very effective in minimizing the change in $PaCO_2$ due to a mismatch between $\dot{V}_E$ and $\dot{V}CO_2$. These results have important implications for the manner in which we think about the nature of the exercise stimulus. Supported by NIH Grant HL 20574 and HL 26091.

12.4

RESPIRATORY AFFERENT ACTIVITY IN THE SUPERIOR LARYNGEAL NERVE (SLN).
O.P. Mathew, F.B. Sant'Ambrogio, G. Sant'Ambrogio and J.T. Fisher. University of Texas Medical Branch, Galveston, Texas 77550.

This study evaluates the afferent activity in the SLN during breathing as well as during occluded inspiratory efforts. Experiments were performed in 9 anesthetized and spontaneously breathing dogs. Electroneurographic activity was recorded from the peripheral cut end of the SLN. A tracheal cannula with a side arm allowed the by-pass of the larynx during breathing and during the occluded efforts. A clear inspiratory modulation was present in all experimental conditions. Both peak and duration of the SLN activity decreased slightly (86% and 91%) when breathing was diverted from the upper airway to the tracheostomy. Peak and duration of the SLN activity (as % of upper airway breathing) increased during occluded efforts; however, the increase was greater when the larynx was not bypassed (peak = 111% vs 195%; duration = 149% vs 169%). Laryngeal paralysis by bilateral section of the recurrent laryngeal nerves reduced the inspiratory modulation both during breathing and occluded efforts. Our results indicate that both collapsing pressure in the larynx and contraction of laryngeal muscles are important in activating laryngeal afferents. The greater increase in SLN afferent activity during upper airway occlusion as compared to tracheal occlusion presumably mediates the reflexes affecting breathing pattern and upper airway patency.
Supported by NIH grants HL-20122 and HL-01156.

12.5

COMPARISONS OF THE EFFECTS OF LUNG RECEPTOR ACTIVATION ON HEART RATE, BREATHING FREQUENCY AND TRACHEAL SMOOTH MUSCLE ACTIVITY. R.L. Coon and E.J. Zuperku. Depts. of Anes. & Physiol., Med. Col. of Wis. & Wood VAMC, Milwaukee, WI 53193

Lung receptors with medullated afferents have been shown to affect breathing frequency (BF), heart rate (HR) and tracheal muscle activity (TMA). The purpose of this study was to compare the effects of lung receptor stimulation on these parameters in the same preparation. Dogs anesthetized with sodium pentobarbital were placed on cardiopulmonary bypass. Vagal efferent output was increased by either increasing the perfusion pressure of the separately perfused carotid sinuses or by switching the perfusate to venous blood. Pressure changes in the water filled endotracheal tube cuff were used as an indication of changes in TMA. Airway pressure and % CO_2, carotid sinus, systemic arterial and tracheal balloon pressures, ECG, and diaphragm EMG were recorded. Diaphragm EMG was used to trigger ventilation of the lungs. Lung inflation patterns were ramp, static or oscillatory. HR decreased and TMA increased during apnea produced by static lung inflation. In the absence of spontaneous ventilation, an oscillatory pattern of ventilation increased HR and decreased TMA. Atropine blocked both the HR and TMA responses. This study suggests that the reflex control of vagal efferent output to both the heart and trachea may be mediated by the same pulmonary receptor type and that phasic rather than static lung inflation is a more effective stimulus. (Supp. by the VA Medical Service).

12.6

DOES BACKGROUND ACTIVITY IN AFFERENT VAGAL C-FIBERS FROM THE LUNGS INFLUENCE BREATHING PATTERN? T.E. Pisarri*, J. Yu*, H.M. Coleridge, and J.C.G. Coleridge. CVRI, UCSF, San Francisco, CA 94143.

In chloralose-anesthetized dogs, breathing spontaneously, we slowly cooled the cervical vagus nerves to determine whether background activity in unmyelinated vagal afferents influenced breathing pattern after conduction in myelinated fibers was blocked (6°C). Vagal cooling to 7°C increased V_T and T_I significantly but T_E was not significantly changed. Cooling to 5°C further increased V_T, but had no significant effect on T_I and T_E. Between 5°C and -1.5°C, V_T, T_I and T_E increased significantly as conduction in C-fibers was progressively blocked. Results of 9 experiments (6 dogs):

	37°C	7°C	5°C	-1.5°C
V_T (ml)	419±64	512±82	548±94	634±91
T_I (s)	0.9±0.1	1.7±0.5	1.8±0.2	2.2±0.1
T_E (s)	4.8±1.1	4.7±0.8	4.9±0.8	7.4±1.6

To determine whether changes in breathing pattern below 7°C could be attributed to changes in C-fiber input from the lungs, we cooled the pulmonary vagal branches just above the lung hilum in open-chested, artificially ventilated dogs after tying off the branches below the lung. At temperatures below 10°C phrenic volleys no longer synchronized with the ventilator cycle. Cooling to 7-5°C shortened the intervals beween phrenic volleys; the intervals lengthened as the nerves were cooled further or cut. (Supported by HL-07192 and HL-24136.)

12.7

REFLEX RESPONSE TO GRADED STIMULATION OF PULMONARY C FIBERS WITH CAPSAICIN. J. Richard Coast and Sharon S. Cassidy. Dept. of Internal Medicine, Pulmonary Research Division. Univ. of Texas Health Science Center, Dallas, Texas 75235

Stimulation of pulmonary C-fibers (PCF) reportedly causes apnea followed by rapid shallow breathing. However, in intact animals in whom PCF are stimulated by injecting a stimulating compound into the right atrium, rapid shallow breathing could be caused by CO_2 retention during apnea or by systemic circulation of the compound. This series of experiments was performed to determine whether rapid shallow diaphragmatic contractions (DC) follow cessation of DC after stimulation of PCF in an *in situ* isolated lung preparation. In open-chest dogs, the left pulmonary artery and veins were cannulated and ventilation was directed to the right lung via a divided tracheal tube. The right hilar vagus was severed to prevent entrainment of DC with the ventilator. A strain gauge and fine wire EMG were placed on the left hemidiaphragm to measure DC and their relationship to electrical activity. Capsaicin was diluted in 50ml of dog blood or dextran and infused at 25ml/min for infusion rates of 6-100 µg capsaicin/min. A dose response was obtained for duration of cessation of DC (0-2 min) and for reduction of strength of DC (0-50%). We found no dose that increased DC or EMG firing even when low enough not to cause cessation of DC. We conclude, therefore, that PCF stimulation alone does not increase rate of DC or EMG firing in a unilaterally isolated lung preparation in dogs.

12.8

ALTERATIONS OF RESPIRATORY CENTRAL PATTERN GENERATOR ACTIVITY WITH FASTIGIAL NUCLEUS STIMULATION. J. L. Williams* and L. O. Lutherer. Departments of Physiology and Internal Med., Texas Tech University Health Sciences Center, Lubbock, TX 79430.

Previous studies stimulating the cerebellum to alter respiration have not made precise measurements of the changes, examined a possible role of the fastigial nucleus (FN), or clearly defined whether these changes were predominantly due to an output to the brainstem or to segmental spinal cord levels. In the present study, electrical stimulation of the rostral fastigial nucleus (chloralose-urethane anesthetized cats) with brief stimulus bursts (0.2-0.3 sec) at 200 Hz, 250 µA during inspiration produced I to E phase-switching as demonstrated by a shortening of the inspiratory phase or an immediate change to expiration. E to I phase-switching was also observed using similar criteria and was confirmed using the analysis of Cohen and Feldman (Fed. Proc. 36: 2367-2374, 1977). Stimulation of these sites for 30 sec at 50 Hz, 150 µA most often elicited an excitatory response as demonstrated by an increased breathing frequency (or decreased T_{TOT}, $P<0.001$) and decreased T_I ($P<0.01$). Tidal volume did not change. Mean inspiratory flow increased ($P<0.01$) indicating altered central inspiratory drive while respiratory timing (T_I/T_{TOT}) was not influenced. These findings suggest that FN is capable of influencing respiratory activity by altering the activity of the primary respiratory central pattern generator. (Supported by AHA grant 82-1235 and Tarbox Institute TTUHSC).

12.9

EFFECT OF DORSAL RESPIRATORY GROUP (DRG) LESIONS ON THE PROCESSING OF VAGAL AFFERENT INPUT IN THE CAT. D.F. Speck, D.R. McCrimmon* and J.L. Feldman, Depts. of Physiology and Anesthesia, Northwestern University, Chicago, IL 60611.

The DRG is often assumed to be an important component in the Breuer-Hering (BH) inspiratory shortening reflex. To test this assumption, the effects of uni- or bi-lateral lesions of the ventrolateral nucleus of the tractus solitarius (vlNTS ≈ DRG) on the BH reflex were examined in anesthetized, vagotomized, paralyzed and artificially ventilated cats. Stimulus trains (20-60 µA, 100 Hz, 0.1 msec pulses) delivered to the vagus nerve during inspiration produced a current dependent shortening of inspiratory duration (TI). A linear array of 2 to 4 tungsten electrodes (tip separation of 0.7 - 1 mm) was positioned in the middle of recorded DRG inspiratory unit activity. Lesions were made by passing direct current (20 µA for 60 sec, electrode negative) through each electrode and between adjacent electrodes. The stimulus current vs. TI relationship was determined before and after lesioning. The relative shortening of TI in response to vagus nerve stimulation at a given intensity was unchanged by DRG lesions. Histological verification of lesion placement indicated >80% destruction of the vlNTS. We conclude that neuronal pathways exclusive of the DRG are sufficient to produce inspiratory termination in response to activation of pulmonary stretch receptor afferents. (Supported by NIH grant HL-23820, D.R.M. is a Parker B. Francis Fellow of the Puritan-Bennett Foundation.)

12.10

EFFECTS OF HYPERCAPNIA AND HYPOXIA ON THE SWALLOWING REFLEX. Takashi Nishino, Toshihide Yonezawa* and Yoshiyuki Honda* School of Medicine Chiba Univ., Chiba 280, Japan.

Reflex swallowing is achieved by the integrated action of the respiratory center and several cranial nerve nuclei under the control of a specific neural group, the swallowing center. Mechanisms integrating swallowing and respiration have been studied both in animals and human beings. However, there is little information about the effects on the swallowing reflex of chemical ventilatory drive factors such as $Paco_2$ and Pao_2 which influence the activity of the respiratory center. We investigated effects of changes in $Paco_2$ and Pao_2 on the swallowing reflex in 12 anesthetized, vagotomized, and paralyzed cats. The swallowing reflex was induced by electrical stimulation of the superior laryngeal nerve (SLN) and was identified by a characteristic brief burst of phrenic nerve (PN) activity and a large amplitude burst of hypoglossal nerve (HN) activity. Steady-state responses to a constant SLN stimulation for 60s were measured at four levels of $Paco_2$ with hyperoxia and at four levels of Pao_2 at a fixed $Paco_2$. Although both hypercapnia and hypoxia increased spontaneous respiratory activity in PN and HN, the number of swallows elicited by SLN stimulation was not influenced by the level of $Paco_2$ whereas a progressive decrease in the number of swallows with decreasing levels of Pao_2 was constantly observed. Our findings indicate that hypoxia depresses swallowing reflex whereas hypercapnia has no effect. (Supported in part by Grant for Scientific Research from MESC of Japan)

13.1

SCALING OF ADDED EXPIRATORY RESISTIVE LOADS: MAGNITUDE ESTIMATION VERSUS HANDGRIP MATCHING. S.R. Muza* and F.W. Zechman. Department of Physiology & Biophysics, University of Kentucky Medical Center, Lexington, KY 40536

Six healthy male adults were studied at five levels of suprathreshold added resistance applied thrice to expiration in a random sequence. Subjects squeezed an isometric handgrip dynamometer coincident with the breath to express the preceived magnitude of the load and also gave a numerical estimate after completing the loaded expiration. Peak mouth pressure, grip deflection and numerical estimate were analyzed to derive the exponents for Stevens' Power Law. The mean exponent and correlation coefficient obtained from numerical estimates were 1.02 ± 0.13 and 0.86 ± .02, respectively, while the exponent and correlation coefficient simultaneously obtained from handgrip matching was 0.60 ± 0.06 and 0.81 ± .07, respectively. Multiplying each subject's exponent obtained from handgrip matching by 1.7 (exponent for sensation of muscle force) yielded a mean equated exponent of 1.03 ± 0.11. The equated exponents were not statistically different from the exponents derived from numerical estimates. We previously reported (J. Appl. Physiol. In Press) similar results for scaling of added inspiratory resistance. Together these results suggest that the use of cross-modality (handgrip) matching provides a reliable method for obtaining psychophysical magnitude functions of respiratory sensations and that exponents obtained using either technique can be equated for comparison. Supported by NIH Grant HL24412.

13.2

EFFECTS OF BILATERAL CAROTID BODY RESECTION ON THE VENTILATORY RESPONSES OF AWAKE RATS TO ACUTE AND CHRONIC HYPOXIA, AND ACUTE HYPEROXIA. E.H. Vidruk and E.B. Olson, Jr. John Rankin Laboratory of Pulmonary Medicine. University of Wisconsin, Madison 53705.

We wished to determine whether the ventilatory responses of awake rats to acute (1hr) and chronic (24hr) hypoxia and acute hyperoxia would be altered by bilateral carotid body resection (CBX). Rats were studied 5hr-64days following either CBX (N=30) or sham surgery (N=17). We used measurements of PaCO2 as an index of ventilatory responses. Following surgery rats with CBX retained CO2 (CBX, PaCO2=48.3±4.1mmHg; Sham, PaCO2=42±2.8mmHg; values are means ± standard deviations). CBX attenuated the ventilatory response to acute hypoxia (CBX, PaCO2=44.5±2.3mmHg; Intact PaCO2=29.2±3.4mmHg). The ventilatory response to chronic hypoxia was eliminated in rats with CBX. At the end of that period their PaCO2=43.5±5.9mmHg compared with intact PaCO2=23±3.1mmHg. In 1hr of normoxia after chronic hypoxia, CBX rats hyperventilated ($PaCO_2$=40.5±5.1mmHg) while ventilation in intact rats returned toward normal ($PaCO_2$=30.0±3.1mmHg). When exposed to 100% O2, rats with CBX hyperventilated (reduced PaCO2 by 4±1.9mmHg) by comparison to Sham rats (PaCO2 reduced by 0.8±1.7mmHg) and intact rats which tended to hypoventilate (increase PaCO2 by 2.2±1.1mmHg). We conclude that CBX alters significantly the rat's normal ventilatory responses to acute and chronic hypoxia, and acute hyperoxia. (Supported by PHS grants HL29043 and HL31430.)

13.3

VENTILATORY RESPONSES OF AWAKE DOGS TO HYPOXIA ATTENUATE HYPOXIC BRONCHOCONSTRICTION. Ronald Sorkness* and Edward Vidruk. John Rankin Laboratory of Pulmonary Medicine, University of Wisconsin, Madison 53705.

We studied three awake dogs each having a chronic tracheostomy. Pressure changes within a water-filled cuff (Pc) on a tracheal cannula were used to measure changes in bronchomotor (BM) tone. Hypoxia-induced reflex bronchoconstriction reportedly occurs in anesthetized dogs. In awake dogs, however, we observed inconsistent changes in BM tone in response to hypoxia (10-12% O2). We hypothesized that hypocapnia and hyperpnea due to the ventilatory response to hypoxia confounded the bronchoconstrictor effect. When isocapnia was maintained with inspired CO2 adjustments, BM tone during hypoxia was greater than when hypocapnia was permitted. In other experiments, while awake dogs were hyperventilated mechanically to prevent changes in rate, tidal volume (VT) and end-tidal CO2, hypoxia consistently caused bronchoconstriction (N=19, median ΔPc=12.5 cm H2O). When a hyperoxic dog was mechanically ventilated first at VT=150ml and then at VT=250ml (using inspired CO2 to maintain isocapnia), BM tone consistently decreased with the larger VT (N=6, median ΔPc=16 cm H2O). We conclude that hypoxia has a primary effect of bronchoconstriction but that in awake dogs hyperpnea and hypocapnia due to hypoxia-induced ventilatory responses can attenuate the primary effect. (Supported by PHS grants HL00780, HL29043 and an AFPE graduate fellowship.)

13.4

CAROTID BODIES ARE REQUIRED FOR VENTILATORY ACCLIMATIZATION TO MODERATE AND SEVERE CHRONIC HYPOXIA. C.A. Smith, G.E. Bisgard, A.M. Nielsen,* L. Daristotle,* N.A. Kressin,* H.V. Forster, and J.A. Dempsey. Univ. of Wisconsin, Madison 53705.

We tested the necessity of carotid bodies (CB) for ventilatory acclimatization to moderate hypoxia and to a level of severe hypoxia known to cause cerebral metabolic acidosis. CBX was confirmed using acute hypoxia, and iv NaCN and dopamine. In normoxia, CBX goats showed partially compensated respiratory acidosis. CBX goats did not acclimatize to moderate hypoxia; their vent. accl. to 2-6 d. severe hypoxia was about one-third that of equally hypoxemic intact goats. After 48 hrs hypoxia, acute normoxia caused reduced hyperventilation in intact goats and slightly increased hyperventilation in CBX goats. In normoxia, serum electrolytes were within the normal range; [Cl-] varied inversely with [HCO3-] during accl. to hypoxia.

	Intact PB=(440mmHg)			CBX PB=(520)			Intact PB=(380)			CBX PB=(450)		
	PO2	PCO2	pH	PO2	PCO2	pH	PO2	PCO2	pH	PO2	PCO2	pH
Normox.	112	36	7.43	100	41	7.42	108	35	7.42	98	41	7.42
1h hypox.	40	33	7.46	45	41	7.42	28	30	7.47	30	40	7.43
48h hypox.	44	31	7.46	43	41	7.41	36	25	7.46	33	38	7.42

We conclude: 1) Carotid bodies are required for a normal time course and magnitude of vent. accl. to chronic hypoxia; and 2) The limited accl. observed in severely hypoxemic CBX goats is most likely mediated by CNS mechanisms that may include transient cerebral metabolic acidosis. USAMRDC & NIH.

13.5

RESPIRATORY SENSATION IN CHRONIC OBSTRUCTIVE LUNG DISEASE. Stewart B. Gottfried*, Susan Redline*, Murray D. Altose. Cleveland Metropolitan General Hospital, Cleveland OH 44109

The psychophysical technique of magnitude scaling was used to evaluate the sensation of external resistive (RL) and elastic (EL) ventilatory loads as well as inspired volume and static inspiratory muscle force in 14 patients with COPD and 12 normal subjects of similar age. The exponents for magnitude estimation of RL and EL were 0.76±0.07 (SE) and 0.92±0.04 (SE) respectively, in normals. Values in COPD were reduced to 0.44±0.04 for RL and 0.64±0.06 for EL ($p<0.05$). Peak inspiratory mouth pressure and inspiratory duration increased progressively with increasing loads but were no different between groups. Exponents for the power function relationship between sensation intensity and peak inspiratory mouth pressure, corrected for inspiratory duration, were 1.47±0.12 and 1.52± 0.17 during RL and EL, respectively, in normals. Exponents were reduced in COPD to 0.92±0.17 during RL and 0.96±0.17 for EL ($p<0.05$). Magnitude estimation and production of both inspired volume and peak inspiratory mouth pressure during static inspiratory maneuvers were no different in the groups. These findings indicate that although the sensations of respiratory muscle force and thoracic displacement are normal in COPD patients, the perception of ventilatory loads is blunted. This suggests an impairment in the central nervous system processing of separate signals related to force and displacement during loaded breathing.

13.6

ROLE OF NICOTINE IN ACUTE RESPIRATORY RESPONSES TO INHALED CIGARETTE SMOKE IN AWAKE DOGS. L.Y. Lee, R.F. Morton* and D.T. Frazier. Univ. of Kentucky., Lexington, KY 40536.

Our previous study demonstrated that inhalation of cigarette smoke (CS) reflexly induced an initial change in breathing pattern and a delayed hyperpnea (J.A.P. 54:562, 1983). To determine the role of nicotine (N) in eliciting these responses, we compared the acute respiratory responses to CS containing two different levels of N in 24 paired studies on 4 awake chronic dogs. Each low N research cigarette contains 0.42 mg N and 31.8 mg tar and high N cigarette contains 2.32 mg N and 27.8 mg tar. Inhalation of high N CS caused an immediate apnea in two dogs. The duration of apnea reached 219 ± 61% (mean ± SD) of the expiratory duration of control breaths. The apneic duration was markedly shorter (116 ± 4%) when CS of low N was inhaled. In the other 2 dogs, an augmented breath was elicited immediately following inhalation of CS of high N in 8 out of 11 trials, whereas low N CS did not. CS caused a delayed hyperpnea in all 4 dogs: CS of high N increased minute ventilation ($\dot{V}_E$) from a baseline of 2.7 ± 0.4 to 31.5 ± 15.4 l/min after CS, and the increase in $\dot{V}_E$ was significantly smaller with CS of low N (from 2.9 ± 0.8 to 5.7 ± 2.3 l/min). These preliminary studies suggest that the level of N contained in the smoke is an important factor in determining the acute respiratory responses to inhaled CS. (Supported by grants from Kentucky Tobacco Research Board 4A024, 4A025.)

13.7

CARDIO-PULMONARY RESPONSES TO CO_2 IN AWAKE RODENTS. M.J. Wiester, J.L. Tepper*, M.F. Weber*, W.A. Schutt Jr.*, and J.A. Graham*. U.S. EPA, RTP, NC 27711. Northrop Services Inc. RTP, NC 27709. CO_2 stimulation of breathing has been used to enhance detection of early lung changes due to injury or disease. CO_2 challenge is well suited to small animal pulmonary function testing because it is rapid, non-invasive and repeatable. The present work examines cardio-pulmonary responses to 15 min episodes of CO_2 (4% and 8%) interspersed between 30 min recovery periods in guinea pigs (Hartley, 400 g) and rats (Fischer 344, 325g). Carotid artery or intrapleural catheters (4animals/group) were implanted 1 day prior to testing. Pulmonary function was done using a body plethysmograph and a head exposure chamber while cardiovascular testing was done using an acrylic exposure box. Results showed that all animals responded to CO_2 with concentration related increases in ventilation that were reflected in increases in tidal volume, breathing rate and flow. Inspiratory and expiratory times were unaltered but apnea times showed concentration related decreases. Guinea pig expiratory resistance was elevated 40% in low and 100% in high CO_2. Rat mean blood pressure increased 12 mm Hg and heart rate fell 15% in 8% CO_2. In both species, PO_2 increased for all CO_2 exposures but PCO_2 increased and pH decreased only at 8% CO_2. All measurements returned to baseline within 30 min. Data indicates that 15 min exposure to 4% CO_2 only augments ventilation in unanesthentized rats and guinea pigs whereas exposure to 8% produces adverse physiological effects that may confound interpetation of lung changes due to injury.

13.8

RESPIRATORY EFFECTS AND SITE OF ACTION OF NICOTINE IN THE CAT. K.A. Westphal*, S.K. Hall*, G. W. Garriss, III*, L.Y. Lee and D.T. Frazier. Dept. of Physiol., Univ. of KY, Lexington, KY 40536.

The effects of nicotine (I.V. 1μg/kg and 5μg/kg) on respiratory control were examined in thiopental-anesthetized cats. The relative contributions of various control mechanisms were studied by comparing the effects of nicotine injections before and after bilateral vagotomy and surgical denervation of the carotid body chemoreceptors. Diaphragm EMG activity was monitored using hook electrodes in the crus. Respiratory $\dot{V}$, V, P_{TP}, CO_2, and arterial pressure were also recorded. In the intact animal, 1 μg/kg nicotine did not significantly change respiratory frequency, although there was a tendency to show a decrease in T_I and T_E. Following bilateral vagotomy there was a significant increase in frequency ($P<.05$) as a result of a significant decrease in T_I. Subsequent denervation of the carotid bodies again shows a significant increase in frequency, but in this preparation the predominant effect was a significant reduction in T_E. Arterial blood pressure profile included hypotension followed by hypertension with bradycardia. In all cases, nicotine resulted in hyperpnea. With 5 μg/kg, all parameters changed in the same direction with greater intensity and duration. The data suggest that nicotine can alter respiratory frequency in the absence of vagal and carotid body afferents. Supported in part by THRI 4A024, 4A025.

13.9

EFFECT OF DIAPHRAGMATIC C-FIBER STIMULATION ON VENTILATION IN THE DOG. D.T. Frazier, W.R. Revelette, and L.A. Jewell*. Dept. of Physiol. and Biophysics, Univ. of Ky., Lexington, KY 40536. This study tested the possible influence of diaphragmatic C-fibers on the control of ventilation. Dogs were anesthetized and intubated with a tracheal cannula. The left femoral artery and vein were also cannulated. The circulation to the left crus, the left phrenico-abdominal artery and vein, were exposed and cannulated. Crural perfusion was maintained by coupling the left femoral arterial and phrenico-abdominal catheters. Myoelectric activity of the left crus and left posterior cricoarytenoid (PCA) was recorded. C-fiber stimulation was accomplished by injection of capsaicin into the phrenic arterial catheter (0.125, 0.25 and 1.0 mg) while recording tracheal airflow, $\%CO_2$ and both raw and averaged crural and PCA electromyograms. Capsaicin infusions of .25 and 1.0 mg were associated with immediate apneusis lasting approximately five seconds consisting of a tonic increase in crural and PCA emgs. Following apneusis, inspiratory airflows and volumes returned to control levels with low level tonic crural and PCA activity still present. Bilateral vagotomy did not eliminate apneusis. Systemic capsaicin injection (1 mg) was associated with a short period of apnea followed by hyperpnea, with no increase in tonic crural or PCA activity. These data suggest that crural C-fiber excitation facilitates medullary inspiratory neuronal activity. Suppported in part by THRI #124.

13.10

ELECTRICAL RESPONSE OF THE DIAPHRAGM TO TILTING AND TRACHEAL OCCLUSION IN THE CAT. W.R. Revelette and D.T. Frazier. Dept. of Physiol., Univ. of KY, Lexington, KY 40536.

This study assessed the influence of altering the mechanical efficiency of the diaphragm and airway occlusion on costal and crural diaphragmatic activity. Cats were anesthetized and intubated with a tracheal cannula. Airflow, $\%CO_2$, and both raw and electronically averaged left costal and crural emgs were recorded. The animals were mounted in a spinal suspension frame so that the thorax and abdomen were not impeded during the respiratory cycle. Changes in diaphragmatic length were accomplished by tilting the animal while in the frame. The electromyographic response to end expiratory tracheal occlusion was tested in three positions, 20° head-down (-20°), no tilt (0°) and 20° head-up (+20°) in the intact, C-7 spinalized (S) and the spinalized + bilaterally vagotomized (S + V) preparation. The results suggest that changing the length of the diaphragm affects costal and crural activity. The +20 position was associated with an increase in peak averaged emg across conditions. Tracheal occlusion produced an increase in inspiratory time (T_I) and peak averaged EMG in the intact and S conditions. With occlusion in the S + V condition, (T_I) was elevated. These results suggest that diaphragmatic afferents participate in regulating regional muscle activity and imply that in the absence of vagal and intercostal afferent information, might affect ventilatory timing. Supported in part by THRI #124.

NEUROBIOLOGY

14.1

SENSORY ADAPTATION IN SPINAL CORD INJURED MALES. Rhonda Comrie* and Marilyn Rubin. St. Louis University, St. Louis, MO 63104

This experimental study examined the effects of touch on spinal cord injured males (N=10). Subjects were touched in an area with sensation and in an area without sensation. Measurements were made of the dependent variables of blood pressure, heart rate, and respiratory rate. Significant findings were noted for two of the dependent variables. First, when the subject was able to feel the touch, the heart rate showed significant change ($p=.05$). This occurred when touch was applied to an area with sensation as well as to an area without sensation. When touch was applied to an area without sensation, heart rate showed statistical change ($p=.01$). Secondly, systolic blood pressure changes, when touch was applied above the level of injury, were statistically significant ($p=.025$) in comparison with systolic blood pressure changes when subjects were touched below the level of injury. It is concluded that physiologic changes related to touch present one measure of assessment of an individual's adaptation to spinal cord injury.

14.2

HISTOCHEMICAL CORRELATES OF BEHAVIORAL EFFECTS OF ALPHA-2 ADRENEREGIC AGONIST IN SPINAL RATS

N.E. Naftchi, R. Lehrer* and J. Sleis* N.Y.U. Med. Ctr., New York, N.Y. 10016 supported by Edmund, Murry and Leone Guggenheim Clin. Research Endowment;

Transection of spinal cord at the level of T_5 vertebrae in Sprague Dawley rats caused dissappearance of the biogenic amine, norepinephrine (NE) and 5-hydroxytrvptamine (5-HT) from the distal stump and their accumulation above the lesion and in the brain stem. These animals dragged their hind limbs (HL), with the dorsum generally touching the ground and plantar surface facing upward. In contrast to these random spastic movements in the untreated control rats, some of the rats treated with an alpha-2 agonist developed a locomotion of HL coordinated with front limbs and used the plantar surfaces of HL for weight bearing. Electrostimulation of the tail also resulted in vocalization in the treated rats. Histofluorescence studies of biogenic amines show that there is a return of fluorescence below the level of the lesion in the intermediolateral cell columns of the treated animals. Furthermore, injection of HRP at T_{10} caused accumulation of the label at the level of the scar (T_5) in the untreated rats. In the treated rats, however, in addition to the build up at the lesion site, HRP was also found in the brain stem. These observations indicate a reactivation of the descending monoaminergic pathways involved in locomotion and the reestablishment of the ascending nociceptive pathways due to treatment with alpha-2 adrenoceptor agonist.

14.3

CORRELATION OF FAR FIELD POTENTIALS AND BRAIN STEM UNIT RESPONSES IN THE CAT. M.A. Cordova-Salinas*, J.G. Blackburn, and S. Trojanowski*. Department of Physiology, Medical University of South Carolina, Charleston, S.C. 29425.

Far field somatosensory evoked potentials and unit responses were recorded in cats. Adult cats were anesthetized with nitrous oxide, paralyzed with pancuronium bromide and placed on a respirator. The left sciatic nerve was exposed and stimulated at a frequency of 1 Hz, 0.3 ms duration and 3 mA intensity. Far field potentials (FFPs) were recorded from a steel screw electrode located in the mid-line of the skull at APo. FFPs were also recorded from the contralateral somatosensory cortex. The reference electrode was placed on the ipsilateral ear and the ground electrode on the contralateral ear. The potentials were amplified, summated with a microprocessor (256 responses) and displayed on a digital plotter. Single unit responses were recorded from the nucleus gracilis, amplified and displayed on the digital plotter. Four stable components were identified in the far field recordings. The mean latencies (± SD) were: 5.53 ± 0.60, 7.60 ± 0.71, 10.05 ± 0.58, 12.17 ± 0.40 msecs. The mean latency of single unit responses was 7.85 ± 0.47 msec. Unit discharge appears to correlate with the second component of the far field response (7.60 ± 0.71 msec), indicating that this component may be generated in the brain stem. Further studies will be required to identify all of the various components of the FFP. This investigation was supported by NINCDS grant 2P01 NS1106610.

14.4

VISUAL RECOVERY IN GOLDFISH FOLLOWING UNILATERAL OPTIC TECTUM ABLATION: EVIDENCE OF COMPETITION BETWEEN OPTIC AXONS FOR TECTAL TARGETS. Barbara E. Schlumpf and Roger E. Davis. (SPON: K.T. Borer). Univ. of Michigan, Ann Arbor, MI 48109

Anatomical studies suggest that regenerating optic axons which invade the ipsilateral lobe of the optic tectum following ablation of the contralateral lobe compete with resident optic axons for synaptic sites on tectal neurons (Springer, A.D. & Cohen, S.M., Brain Res., 225:23, 1981). Invader axons are initially uniformly distributed over the tectal lobe and subsequently become localized in bands separated by areas innervated mainly by resident axons. When the resident axons are destroyed by eye-removal at the time of the tectal ablation, the invader axons remain continuously distributed. We investigated the relationship between the segregation process and the time to recovery of visual function by the invader axons. The index of vision was a branchial suppression response to a moving spot of light that was classically conditioned to an electric shock stimulus. The minimum time to reappearance of vision following ablation of the contralateral lobe of the tectum in two-eyed fish was similar to the reported time of onset of the segregation process. Visual recovery occurred sooner when the opposite eye was removed. These results support the thesis that the invader axons must compete with the resident optic afferents for targets.

14.5

THE RELATIVE IMPORTANCE OF AFFERENT INPUTS FOR POSTURAL CONTROL UNDER LOW LEVELS OF ALCOHOL. A Bhattacharya*, R. Morgan* L. Wang*, and R. Shukla*. (SPON: E.C. Foulkes). Dept. Env. Health, Univ. of Cincinnati, Cincinnati, OH 45267.

In order to quantify the relative role of the participating afferent systems in the control of postural sway induced by low levels of alcohol ingestion, experiments were designed where afferent signals from eyes, proprioceptors, cutaneous receptors, and the vestibular apparatus were modified. Ten male (mean age: 26±.9 S.D. yrs) and ten female (mean age: 26± .4 S.D. yrs) subjects' postural sways were monitored using a multiaxis force platform before and after ingestion of three drinks (.33 ml/kg BW) of 100 proof Vodka in orange juice given every 30 minutes. The sway was described using parameters of mean radius, (R), max. radius (Rm) and the area (A) of sway. Subjects were exposed to four postural tasks of 30 seconds each: feet on platform with eyes open (EO) and eyes closed (EC), feet on 10 cm foam with eyes open (FO) and eyes closed (FC). Such testing procedure allowed indirect challenging of most of the afferent systems. The protocol was approved by the Human Investigations Committee. The results suggested that only vestibular system was affected at .02% Blood Alcohol Concentration (BAC) for males and .03% BAC for females, as characterized by increase (30%) in Rm (task FO) for males and increase (23% and 26%) in R and A for females (task FC). This finding of selective effect of low levels of alcohol on the vestibular system is consistent with previous in-vitro animal study.

14.6

ORIGIN AND PERSISTENCE OF AXONOLOGY. Louise H. Marshall. Brain Research Institute, UCLA, Los Angeles, CA 90024.

The knowledge of the axon has been a subspecialty of neurophysiology since Alexander Forbes at Harvard proposed in jest the term "axonologists". He applied that name to the researchers who gathered to discuss their common interests the evening prior to the 1930 annual meeting of the American Physiological Society, held that year in Chicago. The axon was described in 1836 by Robert Remak at the University of Berlin, who called it the "primitive tube". In the third century B.C., nerve trunks were first described by Erasistratus, the most important neuroanatomist of the era and a member of the Alexandrian School. In the 1920s and 1930s, the axonologists worked intensively on nerve conduction, and the group became too large to meet for dinner and a "prolonged chat". The axon of the giant squid facilitated the pioneering studies of Kacy Cole and served Hodgkin and Huxley well in their analysis of the events surrounding propagation of the nerve impulse. Today the axon is still prominent in neurophysiologic research. For example, most of the information on sodium channels, as well as the knowledge of the nutrition of the neuron, has come from studies of the axon.

14.7

REGIONAL DIFFERENCES IN ABDOMINAL EMGS DURING LEG LIFT AND MAXIMAL VOLUNTARY EXPIRATORY EFFORTS. C. F. Shaw* and Beverly Bishop. Dept. Physiol., SUNY at Buffalo, Buffalo, NY 14214

We compared surface recorded EMGs from external oblique (EO), internal oblique (IO) and rectus abdominis (RA) during leg lift (LL) alone, a maximal voluntary expiratory effort (MVEE) alone and in combination. We reasoned that the level of muscle activity would reveal regional differences in the way spinal motorneurons integrate descending signals initiated by these voluntary acts. Six volunteers lifted and held both legs 15° from the table, performed an MVEE against an occluded tube and combined LL and MVEE maneuvers.

Table 1. Abdominal Activity During LL, MVEE and LL+MVEE

	Changes in IEMG from control in arbitrary units			
MUSCLE	LL	MVEE	Combined LL&MVEE	Algebraic Sum (LL+MVEE)
EO	9.7	8.3	17.2	18.1
IO	11.8	14.3	22.0	26.0
RA	13.0	5.4	20.3	18.4

The results indicate that combined acts produce higher activity in all three muscles than either act alone. EO and IO activity during combined LL and MVEE were not significantly different from the algebraic sum of the two acts performed separately. In contrast, activity in RA during the combined action was significantly higher ($p<0.05$) than during either act alone. We conclude that the abdominal muscles do not behave as a functional unit, but rather are programmed differently for expiratory and non-expiratory motor acts.

14.8

LONG-TERM STIMULATION OF THE SIPHON/GILL REFLEX ALTERS MOTOR NEURONAL FUNCTION OF L_7 IN OLD APLYSIA. J.F. Zolman* and B. Peretz, Univ. of Kentucky Coll. of Med., Lexington, KY 40536.

With increased age L_7 elicited gill-pinnule contractions are significantly decreased as is transmission at pinnule junctions. Reduced activation of the L_7 pathway in pinnules may result in decreased function of L_7 in old Aplysia (Peretz et al., 1984). To test this proposal, the gill/siphon reflex, which involves the L_7-pinnule pathway, was stimulated in freely moving old animals.

Twenty Aplysia, ca 205 days old, were divided into trained and untrained groups. A 1s water jet stimulus, 25 g, was administered to the siphon 10 times/day at 20 min intervals. Ten animals were trained for 3 weeks following which both trained and untrained animals were tested for habituation of the reflex in response to 10 water jet stimuli, 5 g, given 30s apart. During training a significant increase in the duration of siphon contraction was observed. Trained animals also habituated significantly less to rapid stimuli applied to the siphon compared to the untrained animals. After habituation, spike trains in L_7 were produced by 3s depolarizing pulses, and pinnule contraction and junctional transmission were measured in reduced preparations. Both pinnule contraction and facilitation by L_7 increased significantly in trained as compared to untrained old animals. Results suggest that in old Aplysia repeated activation of the gill/siphon reflex alters L_7 function and that decreased pinnule contraction involves decreased use of L_7-pinnule pathway (NIMH, NIA).

14.9

KINETIC AND AUTORADIOGRAPHIC CHARACTERIZATION OF INSULIN RECEPTORS OF BRAIN NEURONS IN CULTURE. Frederick T. Boyd, Jr.*, Thomas F. Muther*, Derrell W. Clarke*, Michael S. Kappy*, Mohan K. Raizada. University of Florida, Gainesville FL 32610

Insulin and insulin receptors have been identified in the brain and various functions have been proposed for an endogenous brain insulin system. However, the cell type(s) in the brain which possess insulin receptors have not been identified. In these studies we have visualized the neuronal insulin receptor using light microscopic autoradiography (LMA) and have characterized the receptor in neuronal brain cell cultures. Neuronal cultures were prepared as previously described (Exp. Cell Res. 143, 351, 1983). These cultures contained 70-80% neurons. Binding of ^{125}I-insulin to these cultures was rapid with a $t_{1/2}$ of association of 5 min and reaching equilibrium binding within 60 min @24 C. The $t_{1/2}$ of dissociation was 15 min and 95% of bound ^{125}I-insulin dissociated from neurons within 60 min. Scatchard analysis revealed a high affinity binding site with a K_d of 0.5 nM and 1.7×10^5 sites per cell. The receptor was specific for insulin with structurally related peptides competing for binding according to their known biological activity. LMA of ^{125}I-insulin bound to these cultures revealed localization of label exclusively on cells with distinctive neuronal morphology. The grains were concentrated on the cell soma as well as on the neurites. There was very little background labeling, indicating that most of the labelled insulin bound to these cultures was bound to neuronal cells. These results indicate that neuronal cells in culture possess specific insulin receptors; this is consistent with a proposed neuromodulatory role of insulin in the CNS. Supported by NIH grant HD 16722.

14.10

PLASMA B-ENDORPHIN CONCENTRATIONS INCREASE WITH THE SEVERITY OF PORCINE HYPOVOLEMIC SHOCK. J.L. PETERSON* and L.R.DEGUZMAN* (SPON: J.D.O'BENAR). LETTERMAN ARMY INSTITUTE OF RESEARCH, SAN FRANCISCO, CA. 94129

Plasma B-Endorphin concentrations (Radioimmunoassay) increase in hypovolemic shock. We compared the B-Endorphin concentrations in a fixed volume (54 ml/kg) unanesthetized, unintubated, porcine hemorrhage model. Blood was removed over 60 min. (50% Total Blood Volume, 50% TBV) and 15 min. (60% Total Blood Volume, 60% TBV). Samples were taken immediately following hemorrhage (0), 60 min. post hemorrhage recovery (R1) and 120 min. post hemorrhage recovery (R2). Samples were treated with heparin (200 USP units/ml), protease inhibitor Aprotinin (5.2 TIU/ml), and frozen (-80°C) until assay. The results (pg/ml) were compared (+SEM). Significant ($p<.01$) effects within (~) and between (*) groups are shown.

	Control	0	R1	R2	
50% TBV	44±5	178±18~	97±11	67±20	n=20
60% TBV	49±4	295±36~*	234±29~*	84±14	n=10

Although B-Endorphin levels increase, no conclusions about cause and effect relationships can be made.

14.11

IS THE ARCUATE NUCLEUS INVOLVED IN THE REGULATION OF THE VASOPRESSIN [AVP] SYSTEM ? R. Gerstberger* and N. Barden* (SPON: H.T. Hammel). CHUL, Quebec, Canada G1V 4G2

Monosodium glutamate [MSG] injected subcutaneously in neonatal rats causes destruction of the arcuate nucleus [ARC] and of some circumventricular organs [CVOs]. The presence of osmoreceptors and the vicinity of the paraventricular and supraoptic nuclei [PVN, SON] make it possible that MSG lesions of the ARC and CVOs influence the vasopressin system. In control rats a 60 hrs dehydration led to increases in blood pressure and plasma AVP whereas the AVP content in the posterior pituitary decreased. Plasma prolactin and ACTH as well as AVP concentrations in the PVN and SON showed no significant alterations. The turnover of dopamine as measured by HPLC strongly increased in the ARC, partially in the PVN and not at all in the SON. MSG treatment caused an elevation in blood pressure and plasma concentrations of AVP and prolactin. Neurohypophyseal and SON content in AVP were diminished and dopamine turnover was consistently decreased in the ARC but not PVN or SON. In the MSG treated animals dehydration did not alter any of the measured parameters. Therefore MSG seems to act indirectly on the SON - posterior pituitary axis thereby strongly reducing regulatory responses of the vasopressin system after osmotic stresses like dehydration.

14.12

INTRACELLULAR/EXTRACELLULAR RATIOS FOR Cl AND HCO_3 ACROSS APICAL AND BASOLATERAL MEMBRANES OF IN VIVO CHOROID PLEXUS AFTER ACID-BASE DISTORTIONS. V. A. Murphy* and C. E. Johanson* (SPON: J.W. Woodbury). Dept. of Pharmacology, Univ. of Utah, Salt Lake City, UT 84132.

Cl/HCO_3 exchange transport is thought to be present in the choroid plexus (CP). In this study, CP was analyzed to determine the relationship between Cl and HCO_3 in CSF, interstitial fluid (ISF), and CP cell after changes in ISF pH or carbonic anhydrase inhibition (CAI). ISF pH was modified by administration of either HCl, NH_4Cl, or $NaHCO_3$ IP. Acetazolamide, 25 mg/kg IP, was used for CAI. Rats were nephrectomized prior to injection of drugs. CSF, plasma, and lateral or fourth ventricle CPs were sampled 1 hr after treatment. pH of both CSF and CP was determined by C-14 dimethadione distribution. CP $[HCO_3]$ was calculated using CP pH and the average of PCO_2 values in CSF and plasma for cell PCO_2. $[Cl]cp/[Cl](csf\ or\ isf)$ was unchanged by metabolic acid-base changes. $[HCO_3]cp/[HCO_3]csf$ was likewise unchanged; however, $[HCO_3]cp/[HCO_3]isf$ was increased in acidosis and decreased in alkalosis. The [Cl] ratios were constant while the $[HCO_3]$ ratios were both increased after CAI. The data imply that [Cl] ratio is well regulated despite CAI or changes in ISF pH. $[HCO_3]$ in CP follows that in CSF more than ISF which suggests the basolateral membrane of CP is where HCO_3 is regulated during metabolic acidosis or alkalosis. CAI appears to alter HCO_3 exit from CP as this would increase both $[HCO_3]$ ratios. Supported by NIH Grant NS 13988.

14.13

SEROTONIN AS A POSSIBLE MEDIATOR OF THE ANTICONVULSANT ACTIVITY OF BENZODIAZEPINES. Larry M. Leadbetter*, Stanley J. Brumleve and Surendra S. Parmar, Department of Physiology, University of North Dakota, Grand Forks, ND 58202

The role of serotonin (5-hydroxytryptamine) as a neurotransmitter mediator was investigated on the anticonvulsant activity of benzodiazepines. Diazepam administered intraperitoneally in doses of 1 mg/kg and 2 mg/kg provided 34% and 83% protection, respectively, against pentylenetetrazol (90 mg/kg, sc)-induced convulsions in male, albino mice (CF_1). Pretreatment with tryptophan (100 mg/kg, ip) or 5-hydroxytryptophan (100 mg/kg, ip) increased protection by diazepam (1 mg/kg) by 46% and 26%, respectively. Administration of p-chlorophenylalanine (p-CPA; 300 mg/kg, ip) showed a dual effect with increased anticonvulsant activity following a 2-hour and decreased activity following a 48-hour pretreatment. These changes correspond to increased and decreased serotonin levels by p-CPA during pretreatment for 2 hours and 48 hours, respectively. Administration of methysergide (10 mg/kg, ip) for 30 minutes was found to cause decrease in the anticonvulsant activity of diazepam (2 mg/kg, ip) by 33%. Similar effect due to changes in the levels of serotonin were found for the anticonvulsant activity of flurazepam (1 mg/kg and 2 mg/kg, ip) and chlordiazepoxide (2.5 mg/kg and 5 mg/kg, ip). These results have provided evidence for the possible mediation of serotonin in the anticonvulsant activity of benzodiazepines. (Supported in part by Biomedical Research Grant RRO-5407 and Max Baer Heart Grant of Dakota State Aerie Fraternal Order of Eagles.)

14.14

PRESYNAPTIC CHANGES IN NEUROMUSCULAR TRANSMISSION ASSOCIATED WITH TOLERANCE TO THE ORGANOPHOSPHATE PARAOXON. Robert H. Thomsen and David F. Wilson. Zoology Department, Miami University, Oxford, OH 45056

Rats were injected daily with a sublethal dose (0.3 mg/Kg) of paraoxon (diethyl p-nitrophenyl phosphate). Symptoms of organophosphate poisoning included tremors, salivation, diarrhea and loss of body weight. Following 9 to 11 days of exposure, symptoms were greatly diminished or absent and body weight began to increase despite continued treatment with paraoxon and continued depression of acetylcholinesterase. The animals appear to be tolerant. Control animals were injected daily with water. Animals were sacrificed following 1, 5, and 14 injections and electrophysiological techniques were used to assess presynaptic changes in neuromuscular transmission using the cut-muscle preparation of the rat diaphragm. No significant changes in the statistical probability of release or store were observed. Following 14 injections (tolerant animals) the quantal content of the first EPP declined by 28% as compared to controls. The mean quantal content of Epps in the plateau phase of repetitive stimulation was 41 to 55% lower, depending on stimulus frequency, in tolerant animals compared to controls. These changes were not observed following 1 to 5 injections (non-tolerant animals). The decline in quantal release appears to be the result of decreased transmitter mobilization. It is suggested that tolerance is the result of transmitter interactions with presynaptic receptors.

14.15

IMMUNOHISTOCHEMICAL LOCALIZATION OF PHENYLETHANOLAMINE N-METHYLTRANSFERASE IN THE RAT BRAIN. C.W.Coen* (SPON: L.A.Fernandez). Section of Neurosurgery, Yale University, New Haven, CT 06510.

Central adrenaline may regulate several physiological functions including blood pressure and luteinizing hormone (LH) release (Coen & Coombs, Neurosci. 10: 187, 1983). Phenylethanolamine N-methyltransferase (PNMT) catalyses the final step in adrenaline synthesis; its immunoreactive distribution in the rat brain has been examined using a modified PAP method. Immunoreactive perikarya were found in the ventrolateral medulla (C1), the medial aspect of the solitary tract n. (C2), the region of the medial longitudinal fasciculus in the rostral medulla (C3), and the following new sites- the n. prepositus hypoglossi (C4), the locus coeruleus (sparsely) (C5), the caudal magnocellular n. (C6), a region extending from the caudal extremity of the third ventricle mammillary recess to the dorsomedial hypothalamic n. (C7) and the perifornical area (C8). Numerous immunoreactive fibres were seen in each of these areas and at sites such as the intermediolateral column and lamina X of the spinal cord, the dorsal vagal motor n., the area postrema, the dorsal parabrachial n., the ventral central grey, the ventral tegmental area, the paraventricular and rhomboid thalamic n., the central amygdaloid n., the periventricular and arcuate hypothalamic n., the median eminence internal zone, the retrochiasmatic area, the supraoptic n., the parvocellular division of the paraventricular hypothalamic n., the bed n. of the stria terminalis, the median preoptic n. and the preoptic site of the LH releasing hormone-containing perikarya. No immunoreactive staining occurred with primary antisera preadsorbed with PNMT.

14.16

STIMULUS-EVOKED SLOW DEPOLARIZATION OF DENTATE GRANULE CELLS IN VITRO: EVIDENCE FOR A SLOW MUSCARINIC CHOLINERGIC EPSP. Valentin K. Gribkoff* and John H. Ashe. Department of Psychology, University of California, Riverside, CA 92521

The hippocampus, including the dentate gyrus, receives an extensive cholinergic projection from the medial septum [Kimura et al, J. Comp. Neurol. 200 (1981):151], and a recent report indicates that repetitive stimulation of these fibers produces a muscarinic slow depolarization in CA_1 pyramidal neurons [Cole and Nicoll, Science 221 (1983): 1299].

We have intracellularly recorded the responses of granule neurons of the dentate gyrus to stimulus trains in the in vitro hippocampal slice. Repetitive stimulation of fibers in or near the hilar region produces a slow depolarization which can last for several minutes, and is accompanied by a substantial increase in input resistance. In most neurons, production of the slow depolarizations is optimized by stimulation at 20-30/sec. for 5 sec. The resultant depolarization typically obtains a peak level of 3-5mV by 30 sec. to 1 min. following the stimulus train, and returns to previous membrane potential values by 3-6 min.

Microtopical application of the muscarinic antagonists atropine (5uM) or quinuclinidyl benzilate (0.1uM) has no obvious effect on resting membrane potential, but significantly reduces the amplitude of the slow depolarizations. These latter findings suggest that the slow depolarizations are the result of muscarinic cholinergic excitation. Supported by NIH grant BRSG-RR07010-17 to J.A.

17.1

SYNAPTIC TRANSMISSION IN THE CHRONICALLY DECENTRALIZED STELLATE GANGLION OF THE CAT. Zeljko J. Bosnjak and John P. Kampine. Depts. of Anesthes. and Physiology, The Medical College of Wisconsin & Wood VA Ctr., Milwaukee, WI 53193.

This study was designed to determine whether chronic decentralization (3 weeks) of the stellate ganglion would abolish local thoracic reflexes which are generated by stimulation of peripheral nerves (J. Phys. 324:273,'82; Am.J.Phys. 246:R354, 1984). Postganglionic electrical stimulation via the ventral or dorsal ansa subclavia evoked graded synaptic responses in only 15% of the neurons studied. This compares with 80% of the neurons during an acute decentralization of the stellate ganglion. The ansae subclaviae, the T_3 and T_4 rami were also examined under electron microscopy for the extent of Wallerian degeneration. A surprising finding was that the preganglionic stimulation of the cut T_3 ramus also produced graded synaptic responses in 40% of the neurons tested in chronically decentralized preparation, as well an antidromic discharges in some neurons. Thus, a) chronic decentralization decreases, but does not abolish peripheral synaptic input, b) afferent projection is still present in the T_3 ramus despite chronic decentralization with cell bodies either in the stellate ganglion or in the periphery, and c) during the electrical stimulation of the the T_3 ramus (acute or chronic decentralization) not all of the synaptic activity recorded in the neurons of the stellate ganglion is from the central origin.
(Supported by NIH Grant 29192 and the VA).

17.2

CONTRACTION OF AIRWAY SMOOTH MUSCLE EVOKED BY ACTIVATION OF THE CORONARY CHEMOREFLEX IN DOGS. A.M. Roberts, H.D. Schultz, T.E. Pisarri*, H.M. Coleridge, and J.C.G. Coleridge. Cardiovascular Research Institute, UCSF, San Francisco, CA 94143.

Stimulation of chemosensitive vagal C-fibers in the heart reflexly decreases arterial blood pressure and heart rate (coronary chemoreflex). We have attempted to determine whether stimulation of these chemosensitive cardiac afferents also evokes reflex changes in airway smooth muscle tone. In chloralose-anesthetized dogs with open chest we ventilated the lungs through the lower trachea and recorded transverse tension in the posterior wall of an upper tracheal segment innervated only by the superior laryngeal nerves. Stimulation of cardiac chemosensitive C-fibers by injecting capsaicin into the left circumflex (LCx) or left anterior descending (LAD) coronary artery, in doses that had no effect when injected into the right or left atrium, decreased blood pressure and heart rate and increased tracheal tension. Effects were abolished by cutting or cooling (0°C) the lower cervical vagi. Tracheal contraction did not appear to be dependent on the decreased blood pressure. Similar effects were obtained by injecting bradykinin or PGI_2 into LCx or LAD. Capsaicin, bradykinin and PGI_2 stimulate chemosensitive vagal C-fibers in the heart but have no direct effect on cardiac vagal A- or C-fiber mechanoreceptors. Our results indicate that contraction of airway smooth muscle is a component of the coronary chemoreflex evoked by activation of vagal chemosensitive C-fibers. (Supported by NHLBI grants 25847 and 07192.)

17.3

STIMULATION OF PULMONARY C-FIBERS REFLEXLY DECREASES CORONARY ARTERIAL RESISTANCE. Kenneth H. Pitetti* and George A. Ordway. Univ. of Texas Health Sci. Ctr., Dallas, TX 75235

Right atrial injections of capsaicin, a C-fiber stimulant, reflexly decrease heart rate and systemic blood pressure (SBP). It is not known, however, if activating pulmonary C-fibers can also evoke reflex changes in coronary arterial resistance. Therefore, in 7 chloralose-anesthetized dogs, we used a constant flow preparation to assess coronary arterial resistance while activating pulmonary C-fibers. A Gregg cannula was passed through the left common carotid artery until the tip fitted snugly in the left circumflex coronary artery (LCCA). The cannula was perfused with blood from the left femoral artery and blood flow through the cannula was maintained constant with a perfusion pump. Perfusion pressure in the LCCA was measured from a side arm in the cannula, and resistance in that vessel was calculated as the ratio of pressure to flow. Capsaicin (10-20 µg/kg) injected in the right jugular vein, produced significant ($p<0.05$) decreases in heart rate, SBP, LCCA pressure, and LCCA resistance. These responses were abolished by bilateral vagotomy. Capsaicin (10-20 µg/kg), injected into the femoral artery, evoked significant changes in heart rate and SBP before and after vagotomy. Additionally, constricting the inferior vena cava produced a significant decrease in SBP with no change in LCCA pressure or resistance before and after vagotomy. These results indicate that activating pulmonary C-fibers produces a reflex decrease in coronary arterial resistance.

17.4

MECHANISMS OF THE NEGATIVE-TILT-INDUCED BRADYCARDIC REFLEX IN DOG. John J. Furedy*, Donna Shulhan*, David C. Randall & Douglas E. Fitzovich*. Dept. Psychology, Univ. Toronto, Toronto, Canada & Dept. Physiology, Univ. Kentucky, Lexington, KY

The human responds to a 90° negative (head up to head down) tilt with a large magnitude (35 bpm) bradycardia which is non-habituating. The head down tilt has been used as an unconditional stimulus in Pavlovian conditioning (Psychophysiol. 15: 538, 1978) and in biofeedback learning situations to teach bradycardia. Data on the mechanisms of this response are difficult to obtain in man. The following experiment examines this issue in intact, sedated (Innovar-Vet) dogs (n=5). Blood pressure was recorded from a femoral catheter. Left ventricular pressure (LVP) was measured using a Millar catheter tipped transducer advanced from the femoral artery into the heart. The d(LVP)/dt was computed. Data were sampled each second starting 2 seconds prior to the tilt. Heart rate (HR) decreased in excess of 30% in response to the tilt; d(LVP)/dt increased modestly. Results suggest that the bradycardia proper is vagally mediated since bilateral cervical vagotomy abolished the HR change. The onset of the bradycardia appeared to be time-locked to changes in blood pressure, but not to the d(LVP)/dt. The increase in d(LVP)/dt persisted post-vagotomy, and was probably due to changes in cardiac loading or sympathetic autonomic nervous activity. (Supported by NIH grant HL 19343 to the University of Kentucky)

17.5

Frequency Response of Sinus Arrhythmia (RSA) during 45° Tilt. by Judith Ann Hirsch and Friedhart Raschke.* Dept. Physiology, SUNY at Buffalo; Buffalo,NY 14214; and Inst. Arbeitsphysiologie Univ. Marburg; Marburg/Lahn D-3550, Fed. Rep. Germany.

RSA depends on the volume (VT) and frequency (F) of breathing (AJPHA 241:H550,1981). Integrated information from multiple thoracic receptor sites contributes to the resultant RSA. We used passive tilt (TI) and seated (SE) and supine (SU) positions to alter thoracic blood volume and end-expiratory lung volume. Fourteen healthy adults (18-48 yrs) breathed at each of several specified F's (3-48 cpm) and constant VT (25% vital capacity) with end-tidal CO_2 maintained isocapnic. RSA was obtained for each breath from polygraph records. Spectral anlysis of heart-rate time series provided the component of heartrate modulation within the respiratory bandwidth (RHR). RSA and RHR amplitudes were plotted vs F on a log-log scale. At low F, RSA and RHR were relatively large in both SE and TI, but smaller in SU. At higher F, RSA and RHR decreased, with similar slopes, in SE and TI, but this decrease was less in SU. At F=10-20 cpm, SU values were higher that for SE and TI. A secondary peak in RSA was found at F=24-36 cpm. In conclusion, the changes in lung mechanics, venous return and blood volume in TI and SE contribute to low-F RSA amplitude, while in SU these changes result in a smaller RSA. These results suggest that important inputs from pulmonary and thoracic cardiovascular receptors may contribute to RSA amplitude at these breathing frequencies.
(Supported in part by NIH Grant R23HL290302)

17.6

IN VIVO AND IN VITRO NICOTINIC HYPERSENSITIVITY OF INTRINSIC CARDIAC NEURONS IN CHRONICALLY DENERVATED DOG HEARTS. D.C. Smith, D.V. Priola and C. Anagnostelis*. Univ. New Mexico, School of Medicine, Albuquerque, NM 87131 and SUNY, Brockport, NY 14420.

Ten dogs were subjected to total extrinsic cardiac denervation. The negative inotropic responses of their hearts were compared with those of nine controls with respect to ACh (0.1-1.0 ug) and NIC (0.5-100 ug) administered intracoronary. The dogs were on cardiopulmonary bypass, and atrial and ventricular contractility were measured by means of a four chamber isovolumetric technique. At the end of this phase of the experiment, atrial strips were removed for in vitro evaluation of negative inotropic response to ACh ($1x10^{-8}$ M - $1x10^{-6}$ M) and NIC ($1x10^{-6}$M - $1x10^{-4}$ M). Both in vivo and in vitro methods demonstrate a leftward shift of the dose-response curve for NIC in denervated hearts, indicative of denervation hypersensitivity. Little or no hypersensitivity to ACh was seen. Tetrodotoxin significantly reduced the in vitro response to NIC and to DMPP ($3x10^{-6}$ M) but did not alter the response to ACh, implying that NIC and DMPP exert their negative inotropic action by way of parasympathetic intracardiac neurons (ICN). An additional 13 dogs were used only for in vitro studies. There was no difference in response between these dogs and those which were used for both in vivo and in vitro studies. The results confirm the in vivo observation that the ICN become hypersensitive to nicotinic activation following extrinsic denervation.

17.7

DIFFERENTIAL CARDIAC SYMPATHETIC ACTIVITY DURING ACUTE MYOCARDIAL ISCHEMIA. Brett H. Neely and Gilbert R. Hageman. University of Alabama Medical Center, Birmingham, AL 35294.

Sympathetic efferent nerve activity was simultaneously recorded from 2 thoracic cardiac nerves in 7 chloralose anesthetized adult dogs. Efferent innervation patterns were determined from heart rate and strain gauge responses following electrical nerve stimulation. In each animal one nerve was selected that was shown to innervate the posterior ventricle, while the second nerve was demonstrated not to affect this area. Ischemia was produced by snaring a marginal branch or the distal portion of the left circumflex artery for 15-30 min. Activities of the nerves to the ischemic region (IR) and non-ischemic region (NIR) were expressed as a percentage of control and the data was analyzed by an analysis of variance. Nerve activities were adjusted for mean arterial pressure and heart rate. Activity in the IR nerve was observed to decrease at the onset of the occlusion and to progress to a level 78±4% (mean±SE) of control ($p < 0.0001$) at 30 minutes of ischemia. Activity in the NIR nerve was observed to transiently decrease, then increase to 160±15% of control ($p< 0.002$) at 30 minutes of ischemia. Thus, ischemia of the posterior ventricle elicits differential changes in the efferent sympathetic activity to the heart. These changes are characterized by decreases in sympathetic activity to ischemic regions while concomitantly increasing sympathetic activity to non-ischemic regions.
(Supported by Alabama Affiliate-American Heart Association).

17.8

PROSTAGLANDINS AFFECT THE REFLEX CARDIOVASCULAR RESPONSE TO BRADYKININ STIMULATION OF SKELETAL MUSCLE. Charles L. Stebbins*, Randall C. Smith* and John C. Longhurst. Univ. of California, San Diego, La Jolla, CA 92093

We have demonstrated previously that injection of bradykinin (BK) into the uninterrupted circulation of skeletal muscle reflexly activates the cardiovascular system. Since prostaglandins (PG) are capable of sensitizing afferent nerves in skeletal muscle, we examined the possibility that PG, particularly PGE_2, contribute to the cardiovascular response to BK. Therefore, in 3 anesthetized cats we injected BK intra-arterially into the gracilis muscle before and after cyclo-oxygenase inhibition with IV injection of indomethacin (2-5mg/kg). BK stimulation induced increases in mean arterial pressure (MAP) of 17+3 mmHg, maximal dP/dt of 650+236 mmHg/sec and heart rate (HR) 16+6 beats/min. Following indomethacin, increases in MAP and dP/dt were reduced to 5+1 mmHg and 400+161 mmHg/sec, respectively, and HR 11+6 beats/min. In 5 additional cats, intra-arterial injection of PGE_2 (15-25 µg) into the gracilis muscle significantly ($p<.05$) augmented the pressor and contractile response to BK simulation. Thus, prior to PGE_2 injection, BK stimulation increased MAP by 12+1 mmHg and dP/dt by 470+211 mmHg/sec. After PGE_2, BK stimulation induced increases in MAP and dP/dt of 20+1 mmHg and 800+18 mmHg/sec, respectively. We conclude that sensitization of afferent nerves in skeletal muscle by PG is important for the full magnitude of BK-induced cardiovascular reflexes.
(Supported in part by NIH NINCSD NS 20165 and AHA 83-758).

17.9

DO VASOPRESSIN-CONTAINING NEURONS IN THE SPINAL CORD INFLUENCE VASOMOTOR OUTFLOW? J.P. Porter* and M.J. Brody. Dept. of Pharmacology and the Cardiovascular Center, University of Iowa, Iowa City, IA 52242

Neural projections which contain vasopressin extend from parvocellular paraventricular nucleus (PcPVN) to the spinal cord. We sought to determine the role of these peptidergic neurons in modulating vasomotor outflow. Rats were instrumented with Doppler flow probes on the mesenteric and renal arteries and the lower abdominal aorta. The hemodynamic responses produced by PcPVN stimulation were determined before and after intrathecal administration (i.t.) of the vasopressin antagonist, Pmp^1, O-methyl-Tyr^2-[Arg^8]-vasopressin. Peripheral vasopressin receptors were first saturated with i.v. AVPX (20 µg/kg). AVPX (2 nmole in 3 µl, i.t.) decreased arterial pressure (AP) by 10 mmHg and selectively dilated the hindquarters. PcPVN stimulation produced an increase in AP accompanied by mesenteric and renal vasoconstriction. Hindquarter resistance either increased or did not change. After i.t. AVPX, the pressor and constrictor responses to PcPVN stimulation were significantly reduced and the response in the hindquarters was reversed to vasodilaton. Saralasin (2 nmole) given i.t. had no effect on baseline or stimulated parameters. These data suggest that vasopressin-containing neurons in the spinal cord contribute to tonic vasoconstrictor outflow to the hindquarters and to vasoconstrictor responses produced by stimulation of the PcPVN.

17.10

CHARACTERISTICS OF THE HYPERTENSION DUE TO CHRONIC INTRACEREBROVENTRICULAR (ICV) INFUSION OF HYPERTONIC SODIUM CHLORIDE (NaCl). Y. Kawano, R.T. Sudo, R.C. Speth and C.M. Ferrario, Cardiovascular Research Dept., Cleveland Clinic Foundation, Cleveland, OH 44106.

The effects of a 7 day infusion of hypertonic (1.5M) NaCl given via an osmotic minipump into either the third ventricle (3rdV) or a vein (IV) was examined in Sprague Dawley rats. Data were compared to those obtained in rats given isotonic (0.15 M) NaCl into the 3rd V. ICV 1.5 M NaCl (rate: 5 µl/hr) produced mild hypertension (+ 22 ± 5, 1st day vs + 10 ± 3 mmHg, 7th day) and increased water intake and urinary output. Urinary Na^+ excretion and heart rate did not change. By the 7th day, rats given 1.5 M NaCl ICV were hyponatremic and showed a 35% increase in plasma norepinephrine ($p < 0.05$) but not arginine vasopressin (AVP). None of these changes were found in rats subjected to IV infusion of hypertonic NaCl or ICV infusion of 0.15 M saline. To assess the contribution of the sympathetic nervous system (SNS) and AVP to the increases in mean blood pressure (MBP), hexamethonium chloride (Hex.) (20 mg/kg, IV) and an AVP antagonist [$d(CH_2)_5$ Tyr (ME) AVP, 10 µg/kg IV] were given on the 1st and 7th days of the infusion. In rats given ICV 1.5 M NaCl the depressor response to Hex. was always greater than in the control group. The AVP antagonist was effective only on the 1st day. The data suggest that sustained increases in the cerebrospinal fluid level of Na^+ and/or osmolarity, causes mild hypertension predominantly due to activation of the SNS. AVP may play a part in the early, but not the later, stage of the hypertension. (Supported by NHLBI grant, HL-6835).

17.11

CENTRAL HYPOTENSIVE ACTIONS OF ADENOSINE ANALOGS IN THE RAT. R.A. Barraco, R.S. Salah* and J.W. Phillis. Wayne State Univ. Medical Sch., Detroit, MI 48201

Adenosine (ADO), its precursors and the enzymes involved in both its synthesis and degradation are ubiquitous to neural and other tissues. In the CNS, ADO and its analogs exert potent depressant effects on neuronal firing at many levels of the neural axis. ADO is released from neurons and synaptosomes following electrical stimulation and the notion that ADO acts as a synaptic modulator in the CNS is supported by demonstrations of its inhibitory effects on the presynaptic release of a number of neurotransmitters. Perhaps the best characterized effect of ADO at the biochemical level is its capacity to modulate adenylate cyclase activity through two separate purinergic receptors, A_1 and A_2. Male Sprague-Dawley rats with chronic indwelling cannulae were injected in the lateral cerebral ventricle with two adenosine analogs and their effects on blood pressure and heart rate were examined. NECA (5'-N-ethylcarboxamidoadenosine) and L-PIA(L-phenylisopropyladenosine) produced dose-related reductions in blood pressure and heart rate. NECA exerted slightly more potent hypotensive action while L-PIA was more potent in depressing heart rate. These effects were antagonized by intraperitoneal injections of caffeine. These studies on the central effects of ADO analogs on blood pressure and heart rate and their antagonism by caffeine suggest that the CNS areas involved in the control of cardiovascular function may be under the influence of endogenously released purines.

17.12

NONADRENERGIC NONMUSCARINIC CARDIOACCELERATION: IMPACT OF DRUG AND HYDRAULICALLY-INDUCED INCREASES IN AFTERLOAD, J. Evans*, R. Rountree*, D. Randall, & C. Knapp*, M.N. Gillespie*. Univ. of Kentucky, Colleges of Engineering, Pharmacy and Dept. of Physiology and Biophysics, Lexington, Kentucky 40506.

Although a number of studies have demonstrated the existence of vagal nonadrenergic, nonmuscarinic cardioacceleratory pathways, it is not known whether such pathways can be reflexively activated. We, therefore, reasoned that a vagal stimulus such as increased afterload might reflexively provoke tachycardia in atropinized and beta adrenergically blocked dogs. To test this hypothesis we evaluated the chronotropic effects of both phenylephrine (PE) and -2gz acceleration on 6 normally innervated and 7 cardiac denervated dogs. Both groups were chronically instrumented; sedation with Innovar and autonomic blockade were effected just prior to study. PE (25-50 ug/kg IV bolus) increased aortic pressure (AP) by 56 $\pm$ 7 mmHg and produced a 16 $\pm$ 3.5 b/min increase in heart rate (HR) in normal dogs. In denervated dogs, PE-induced increases in AP of 45 $\pm$ 7 mmHg were associated with HR increases of 7 $\pm$ 2 b/min. Acceleration increased AP by 50 $\pm$ 13 mmHg with no accompanying HR response in the normally innervated dogs but produced an 11 $\pm$2 b/min increase in denervated dogs. Ganglionic but not alpha blockade abolished this response. We conclude that nonadrenergic, nonmuscarinic increases in HR can be evoked by increases in afterload but the reflex nature of this response remains unclear. The persistence of the response after denervation that was blocked by ganglionic blockade suggests that the intrinsic chronotropic innervation of the heart may include a nonmuscarinic nonadrenergic, possibly nicotinic, pathway. (Supported by AFOSR 80-0039).

MUSCLE/CEREBRAL CIRCULATION: METABOLIC CONTROL

18.1

THE EFFECTS OF IBUPROFEN ON POST-OCCLUSION HYPEREMIA IN HUMANS. Phillip D. Toth*, Robert J. Demeter*, William V. Judy. Department of Medical Research, Methodist Hospital, Indianapolis, IN 46202.

The role of prostaglandins in post-occlusion hyperemia has been suggested in many studies. The mechanism of the hyperemic response has not been well characterized in humans. The present study was designed to measure both cardiac function and peripheral blood flow as well as characterize the length of inhibition of post-occlusion hyperemia by a prostaglandin inhibitor. Six male volunteers with no cardiovascular disease participated. Cardiac function and forearm blood flows were measured by impedance cardiography. After control data was obtained, arm flow was occluded with a standard blood pressure cuff for 2 minutes. The cuff was then deflated and flows were measured for an additional 10 minutes. After the baseline data was recorded, each subject was given ibuprofen (600 mg p.o.). The post-occlusion hyperemia was observed 2, 5, and 8 hours after ibuprofen administration. No differences were noted for heart rate and cardiac ouput during the control, occlusion, or hyperemic periods throughout the study. Below is listed the forearm flows during the various observation periods:

n = 6	forearm blood flow (ml/100 ml/min)		volume (ml)/beat)	
	control	peak	control	peak
Baseline	10.2 $\pm$ 0.6	29.8 $\pm$ 2.3	0.90 $\pm$ .06	2.62 $\pm$ 0.13
2 Hour	9.7 $\pm$ 0.6	13.5 $\pm$ 0.9*	0.86 $\pm$ .07	1.21 $\pm$ 0.11*
5 Hour	10.9 $\pm$ 0.6	20.2 $\pm$ 1.7*	1.02 $\pm$ .05	1.87 $\pm$ 0.15*
8 Hour	11.8 $\pm$ 0.8	24.9 $\pm$ 1.3	0.97 $\pm$ .08	2.03 $\pm$ 0.17*

*$p \leq 0.05$

These data demonstrated that post-occlusion hyperemia is a peripheral phenomenon and not cardiac in nature. The data also demonstrated that peak forearm blood flows are attenuated for at least 5 hours while the peak volume/beat is still significantly affected at 8 hours after a signle dose of ibuprofen. Studies are in progress to further characterize the length of the attenuated hyperemic response by ibuprofen and correlate this with serum concentrations of the drug.

18.2

TOTAL AND REGIONAL O_2 DEFICIT/EXCESS DURING AND AFTER HYPOXIA WITH METHOXAMINE. Cheryl E. King and Stephen M. Cain. Dept. of Physiology and Biophysics, Univ. of Alabama in Birmingham, Birmingham, AL 35294.

To see whether exaggerated α-adrenergic tone would modulate the accumulation of O_2 deficit by the whole body (WB) and hindlimb (HL) during hypoxic hypoxia (F_{IO2}=0.091) and the subsequent patterns of excess O_2 uptake ($\dot{V}O_2$) during recovery, we infused methoxamine (10 μg/kg·min, i.v.) into 24 anesthetized, paralyzed, pump-ventilated dogs. A 30 min control period of breathing room air was followed by either 15 or 30 min of hypoxia and then a 20 or 30 min recovery period on air. The amounts of O_2 deficit in both the WB and HL were approximately proportional to time in hypoxia. Regardless of O_2 deficit amount, the bulk of WB excess $\dot{V}O_2$ occurred in the first 5 min of recovery. After 15 min of hypoxia, HL excess $\dot{V}O_2$ showed no immediate peak but did resemble the WB pattern more after 30 min of hypoxia. These patterns in HL $\dot{V}O_2$ corresponded to those of post-hypoxic hyperemia which was absent after the 15 min but was present after the 30 min hypoxia. HL O_2 extraction was over 65% in all cases during recovery. Continuous α-adrenergic receptor stimulation decreased HL post-hypoxic flow excess but did not significantly decrease excess $\dot{V}O_2$ during recovery. The difference in pattern between WB and HL suggest that organ systems other than muscle were much less affected by the exaggerated α-vasoconstrictor tone.
(Supported by Grant HL-26927 from NIH)

18.3

EXERCISE HYPEREMIA CORRELATES WITH POTASSIUM RELEASE. M.A. Kapin and E.L. Bockman. Department of Physiology, Uniformed Services University, Bethesda, Maryland 20814

In this report, the correlation of blood flow (BF) with potassium release (K^+R) was examined using a free-flow, vascularly isolated canine gracilis muscle preparation. Muscle (isometric) performance was varied by altering the stimulation frequency. At 20 sec of exercise, BF (range: 18.9 to 34.3 ml/min/100g) correlated highly with K^+R (range: 0.74 to 12.55 μEq/min/100g); r=0.76, P<0.05, (n=8). At 10 min of exercise, BF (range: 24.5 to 71.5 ml/min/100g) remained highly correlated with K^+R (range: -2.76 to 12.88 mEq/min/100g); r=0.80, P<0.02. In a separate series (n=6), ouabain, an inhibitor of the Na^+,K^+-ATPase, was infused (1.25 μg/min; i.a.) prior to and during exercise. At 20 sec of exercise, BF (range: 19.4 to 29.5 ml/min/100g) did not correlate with K^+R (range: 3.4 to 11.8 μEq/min/100g); r=0.09. At 10 min of exercise, there was also no correlation of BF (range: 25.6 to 36.7 ml/min/100g) with K^+R (range: 0.0 to 19.9 μEq/min/100g). Resting BF averaged 14.9±2.7 and 14.5±2.6 ml/min/100g for control and ouabain, respectively. K^+R prior to exercise averaged -0.3±0.2 and 1.9±0.9 μEq/min/100g for control and ouabain, respectively. Thus, a high correlation exists between BF and K^+R under variable levels of muscle performance in saline but not in ouabain-treated preparations. This is consistent with a role for K^+ in mediating free-flow exercise hyperemia in the canine gracilis muscle. (Supported by HL 26345)

18.4

ADENOSINE (ADO) AND EXERCISE HYPEREMIA IN CREMASTER MUSCLE. Kenneth G. Proctor. Dept. Physiol., Univ. Tenn. Ctr. Hlth. Sci., Memphis, TN 38163.

To test whether ADO mediates small arteriolar blood flow (BF) in striated muscle, the microcirculation was exposed to a continuous superfusion (10-30 min) of either a vehicle control, adenosine adeaminase (ADA, 7μg/ml), or theophylline (THEO 10^{-5} M) solution during and following twitch contraction. Perivascular access, persistence, specificity, and dose effectiveness of ADA were demonstrated. BF was estimated with the dual slit method at 10 sec intervals for 3 min before and after 2 min of electrical stimulation at 10, 5 or 2 Hz. The peak and average arteriolar diameter, peak and average BF, duration of the exercise-evoked response, and the total estimated volume of blood delivered in 3 min after exercise were reduced by ADA as a function of stimulus frequency relative to control. ADA reduced total BF by 44, 35, and 22% at 10, 5, and 2 Hz, respectively. Although THEO was more damaging to the tissue at a dose which was equieffective with ADA, it also produced a consistent reduction in peak and average arteriolar diameter and estimated BF after 5 Hz. If small arteriolar BF is proportional to total tissue BF, then ADO may be one mediator of exercise hyperemia whose contribution depends on the intensity of the stimulus. Alternatively, these data could implicate ADO in exercise induced capillary recruitment. Supported by AHA #83-1077 and NIH HL #30663.

18.5

EFFECT OF THEOPHYLLINE ON HINDLIMB BLOOD FLOW AUTOREGULATION IN CONSCIOUS DOGS. P.J. Metting, D.L. Weldy*, T.F. Ronau*, J.R. Strader*, and S.L. Britton. Medical College of Ohio, Toledo, Ohio 43699.

Hindlimb vascular bed pressure-flow (P-F) relationships were obtained in 9 conscious dogs at rest before (control) and after the infusion of 2,4-dinitrophenol (DNP) (0.1 moles/min), and after subsequent administration of theophylline (50 μmoles/min) to block adenosine receptors. External iliac flow was measured with an electromagnetic probe during stepwise reductions in perfusion pressure produced with an occlusion cuff located distal to the flow probe. The efficiency of autoregulation was quantitated by calculating the closed loop gain of flow regulation (Gc) at each pressure decrement as Gc=1-[Fo-Fn/Fo/Po-Pn/Po], where Fo and Po are the starting F and P before each pressure decrease and Fn and Pn are the new F and P at each decrement. The Gc values were negative at each pressure decrement ($\bar{x}$ -0.20 ± 0.06) for the control data and positive ($\bar{x}$ = 0.47 ± 0.05) in the presence of DNP (P<0.05 from DNP; P=N.S. from control). These data demonstrate that the hindlimb vascular bed P-F relationship in conscious dogs is primarily passive at rest, but that autoregulatory behavior predominates when oxygen consumption is increased. This active (autoregulatory) P-F relationship became predominantly passive in the presence of theophylline. These results suggest that adenosine mediates the autoregulatory responses observed in the hindlimb vascular bed in conscious dogs. (Supp. by N.W.OH. A.H.A. and BRS from MCO).

18.6

AUTOREGULATION (AR) OF CEREBRAL BLOOD FLOW (CBF) IN NEWBORN DOGS - EFFECTS OF HYPOXEMIA (H) AND HYPERCARBIA (HC). Uma R. Kotagal and Amy Nathan (Spon. D. Baldwin), University of Cincinnati, Cincinnati, Ohio, 45267.

We studied AR of CBF under conditions of severe hypoxemia (PaO_2 < 20 torr) and hypercarbia ($PaCO_2$) > 80 torr) in paralyzed ventilated newborn dogs using radioactive microspheres. Following baseline measurements, H and HC were produced by altering FiO_2 and $FiCO_2$, and repeat measurements were made. In experimental animals (E), AR was tested by volume depletion to produce hypotension (HT). In control animals no volume alterations were made. During H in E (n=7) CBF (ml/gm/min) increased from .22±.09 to .50±.1 and remained at .50±.05 during volume depletion in spite of a 30%-40% fall in BP and cardiac output (CO). During HC (n = 6) in E, CBF (ml/gm/min) increased from .26±.04 to .51±.22 and remained unchanged at .64±.36 during HT. Thus, when HT is superimposed on H or HC, CBF remains constant suggesting that AR is preserved. The further fall in cerebrovascular resistance seen when HT is superimposed on H or HC suggests that the mechanism responsible for HT vasodilatation may be different from that due to H or HC. (Mean ± SD).

18.7

INTERACTION OF CO_2 AND AMMONIA ON CEREBRAL BLOOD FLOW AND O_2 CONSUMPTION IN DOGS. Raymond C. Koehler, Zohar Barzilay*, Alan G. Britten*, J. Michael Dean*, and Richard J. Traystman The Johns Hopkins Medical Institutions, Baltimore, MD. 21205

Studies of acute and chronic hyperammonemia suggest that cerebral blood flow (CBF) and O_2 consumption ($CMRO_2$) become uncoupled and that $CMRO_2$ may depend on $PaCO_2$. We examined CBF (radiolabeled microspheres) and $CMRO_2$ during hypercapnia ($PaCO_2$ ≈ 74 Torr) and hypocapnia ($PaCO_2$ ≈ 21 Torr) before and during i.v. ammonium acetate infusion in pentobarbital-anesthetized dogs. Continuous infusion over 120 min produced stable increases of arterial ammonia levels (1400 μM/L) by 30 min and no changes in CBF, $CMRO_2$ or O_2 extraction (measured at sagittal sinus) when $PaCO_2$ was held constant (≈ 35 Torr). Acute hyperammonemia attenuated the increase in CBF during hypercapnia by 44% and abolished the decrease in CBF during hypocapnia. Blood flow to pons and midbrain increased 1-2 fold during normocapnic hyperammonemia. Midbrain blood flow increased further during hypocapnia (+131± 51%). Thus, we failed to detect an uncoupling of global CBF and $CMRO_2$ during normocapnic hyperammonemia or an interaction of CO_2 and ammonia on $CMRO_2$, although the increased pons and midbrain blood flow may reflect regional effects of ammonia on reticular activating system metabolism. The attenuated hypercapnic CBF response may arise from impaired glial regulation of ECF K^+ and HCO_3^-, while lactic acid production, enhanced by combined alkalosis and hyperammonemia, may contribute to the abolition of hypocapnic vasoconstriction.

18.8

Post-asphyxic autoregulation (AR) of cerebral blood flow (CBF) in newborn dogs. AJ McPhee*, UR Kotagal*(SPON: LI Kleinman), University of Cincinnati, Cincinnati, OH, 45267.

We studied AR of CBF during post-asphyxic hyperemia in newborn dogs, using volume depletion/repletion to manipulate cerebral perfusion pressure (CPP) and microspheres to measure cardiac output (CO), cerebral hemispheric (CHBF), cerebellar (CeBF) and brainstem blood flows (BrBF).

Following baseline measurements (I), a series of 3 asphyxic insults were produced by temporary cessation of mechanical ventilation. 10 minutes after the third insult, another series of measurements were made (II). Then, AR was tested by volume depletion (III) and repletion (IV) in the experimental group (E), with no volume manipulation in the control group (C). Arterial pO_2 was >80 torr and pCO_2 30-45 torr for all groups and periods. Results (means):

Period	I.		II.		III.		IV.	
Group (n)	E(4)	C(4)	E(4)	C(4)	E(4)	C(4)	E(4)	C(4)
CPP mmHg	61	57	50	47	41	50	51	50
pH	7.35	7.37	7.18	7.19	7.20	7.21	7.20	7.23
CO ml/kg/min	184	180	144	142	83	145	151	167
CHBF ml/100gm/min	37	36	50	50	43	41	48	38
CeBF	57	58	89	81	71	74	93	72
BrBF	84	68	135	133	102	103	114	91

Thus, during hypotension (III), regional CBFs are similar in E and C for all 3 regions, implying functional AR. The reason for increased regional CBFs in E vs. C in IV is uncertain, but may relate to the systemic effects of hypotension in III.

18.9

CHOLINERGIC VASODILATATION IN NORMAL AND ISCHEMIC CEREBRAL CORTEX. Oscar U. Scremin and Erika Scremin* VA Medical Center. Albuquerque. New Mexico. 87108

The cerebral dilator effect of Physostigmine (PHY) was studied in rats anesthetized with halothane and mechanically ventilated. PHY was given intravenously (0.15 mg/kg) and its pressor effect was blocked with Phentolamine (0.1 mg/kg iv). Cortical blood flow (CoBF) was measured with the hydrogen clearance technique from implanted platinum electrodes, 25μm in diameter.

CoBF of normal cortex was 98±(SE)9 and it increased significantly (p<.05) to 203±20 ml/100g·min following PHY (n=5). After permanent occlusion of a cortical branch of the middle cerebral artery, CoBF measured in an area supplied both by that branch and by another from the anterior cerebral artery, decreased to 55±7 ml/100g·min (significantly different from normal cortex, p<.05, n=5). Administration of PHY within 2 hours of arterial occlusion increased CoBF in this area to 155±22 ml/100g·min (significantly different from post-occlusion CoBF, p<.05, n=5). Blood pressure, measured from a cannulated femoral artery, did not show significant variations among the various experimental groups and averaged 88±4 mm Hg (n=15).

It is concluded that there is a reserve for vasodilatation in areas of ischemic cortex that can be uncovered by inhibition of cholinesterase with Physostigmine.

(Supported by Veterans Administration research funds)

18.10

ASPIRIN AND INDOMETHACIN INHIBIT BLOOD-INDUCED VASOCONSTRICTION IN ISOLATED PERFUSED CANINE CIRCLE OF WILLIS. S.A. Lang* G.S. Malindzak, Jr., and M.B. Maron. Physiology Program, N.E. Ohio Univ. Col. Med., Rootstown, Ohio 44272

We have shown that, in an isolated canine brain, the topical application of blood, to the external surface of the arteries comprising the Circle of Willis, produced vasoconstriction. In this study, we tested the hypothesis that prostaglandins mediate this constriction. The brains of 13 dogs were removed, and the large arteries were perfused at a constant flow (avg. 26.0 ± (S.E.) 1.3 ml/min) and outflow pressure (0 mmHg), with oxygenated Krebs-Henseleit (K-H) solution. Under baseline conditions, inflow pressure averaged 76.4 ± 2.8 mmHg, and inflow resistance averaged 3.04 ± .21 mmHg·min·ml^{-1}. In each experiment, blood was topically applied 3 times (Q̇= 6.2 ml/min) followed by a wash of K-H solution. The first and last blood applications were made to obtain control vasoconstriction responses. In the second blood application, either aspirin or indomethacin (10^{-3}M) was added to the blood and perfusate. The results are shown below:

Average Increase in Arterial Resistance Resulting from Topically Applied Blood

	Control	Inhibitor	Control
Aspirin	16.9 ± 2.6	9.2 ± 4.3	22.7 ± 5.1
Indomethacin	22.8 ± 4.3	-0.1 ± 1.2	28.1 ± 7.9

These results thus suggest that, in this preparation, vasoconstrictor prostaglandins may mediate vasoconstriction produced by extravascular blood.

19.1

ANGIOTENSIN II IN BLOOD AND 3rd VENTRICLE CSF OF DOGS ARE INDEPENDENTLY CONTROLLED DURING OSMOTIC THIRST IN CONTRAST TO ANTIDIURETIC HORMONE. Christa Simon-Oppermann* and David A. Gray* (SPON. Rudolf Thauer). Max-Planck-Institute, W.G. Kerckhoff-Institute, D-6350 Bad Nauheim, F.R.G.

The physiological significance of thirst stimulation by centrally applied angiotensin II (AII) has been debated because of the high concentrations necessary to induce this effect. We have investigated how osmotically induced thirst affects endogenous AII concentration in 3rd ventricle CSF and in blood (RIA method) of dogs, collecting CSF with a device used previously in corresponding studies on the antidiuretic hormone (ADH) (Am.J.Physiol. 245: R549, 1983). Simultaneously collected CSF and plasma samples from 5 normally hydrated conscious dogs supplied with a commercially available diet showed AII concentrations not significantly different (32.4 ± 3.5 vs. 40.1 ± 6.9 $pg.ml^{-1}$; means ± SEM, n = 9), while ADH concentrations are 5-10-fold higher in CSF than in plasma. Intravenous infusions of 5% saline (1.5 $mMol.kg^{-1}.min^{-1}$ NaCl) over 38 min, which elevated plasma osmolality by 13.6 ± 1.9 $mOsm.kg^{-1}$, increased both CSF and plasma ADH. AII decreased in the plasma by 8.5 ± 4.4 $pg.ml^{-1}$ ($2P<0.01$) but increased by 8.8 ± 6.3 $pg.ml^{-1}$ ($2P<0.05$) in the CSF (Wilcoxon matched pairs signed ranks test). The observed dissociation of the changes in AII concentration between CSF and plasma during osmotic thirst, in contrast to the parallel changes of ADH concentrations in CSF and plasma, indicates separate control of central and systemic AII formation in dogs.

19.2

CONTINUOUS MEASUREMENT OF CEREBRAL ARTERIOVENOUS DIFFERENCES OF β-ENDORPHIN/β-LIPOTROPIN (β-EP/β-LPH) IN SHEEP. L. S. Leshin* and P. V. Malven. Purdue University, W. Lafayette, IN 47907.

To investigate possible retrograde delivery of pituitary β-EP/β-LPH to the brain, paired samples of blood were collected at 20-sec intervals from carotid artery (CA) and from sagittal sinus (SS) at the point where diencephalic effluent enters. Concentrations of β-EP/β-LPH were measured in each pair of blood samples and in CSF collected from the cisterna magna using a RIA which reacted equally with β-EP and with β-LPH. Whenever β-EP/β-LPH in the SS exceeded its paired CA concentration by an amount greater than random variation, retrograde delivery was considered a possibility. During some trials, increased release of β-EP/β-LPH into plasma was provoked by exogenous naloxone or by live E. coli bacteria. However, there was no concomitant increase in CSF concentrations. Paired arteriovenous differences were examined during 31 periods of 3 to 22 min each. In only 5 of 31 periods was the SS minus CA concentration difference consistently positive. In only 2 of 31 periods did this positive arteriovenous difference also occur during a time of increasing arterial β-EP/β-LPH as would be expected if caused by a major discharge from the pituitary. Therefore, the present results provide little support for retrograde delivery of pituitary β-EP/β-LPH to opiate receptors in the brain without dilution in the systemic circulation. Moreover, the few cases of positive arteriovenous differences may represent diencephalic secretion of β-EP/β-LPH.

19.3

ENDORPHIN LEVELS IN THE HYPOTHALAMUS, PLASMA AND CEREBRAL CORTEX OF BURNED RATS. Paul Nathan and Linda L. Witt.* Shriners Burns Inst. and Univ. of Cincinnati, OH 45219.

The endorphin compounds which act as modulators of both pain sensation and body metabolism were assayed in thermally injured rats. The rats (250 g) were anesthetized and scald burned over a 23 cm^2 area of their backs. Two days postburn the whole brain was rapidly removed and the hypothalamus and cortex were isolated and assayed (Rosier et al. Life Sci. 21: 847, 1977). The results, 2 days postburn, for mean hypothalamic endorphin levels ± the standard error in 19 sham-treated rats was 33.6 ± 3.0 p mols β endorphin/g tissue x 10^4. The mean β endorphin values for 21 burned rats, 2 days postburn was 71.8 ± 7.9 p mols/g hypothalamus x 10^4. The results show a significant ($p < .01$) two-fold increase in the hypothalamic endorphin level in burned rats compared to the sham-treated rats. The plasma levels in control rats was 114 ± 26 p mols/ml, and in burned rats was 104 ± 10 p mols/ml. The mean plasma levels do not differ when comparing burned and control rats. Additional studies in 30 rats showed cerebral cortex and pituitary levels of endorphin were similar in burned and control rats. The increase observed in the hypothalamic concentration of endorphin in the burned rats suggest that the natural opiate system is activated following a thermal injury. Some of the metabolic events associated with burns may be mediated through the endorphins acting in the central nervous system.

19.4

COUNTERACTION OF CYSTEAMINE-INDUCED DECREASE IN PLASMA PROLACTIN BY 5-HYDROXYTRYPTOPHAN. H.H. Ahmed*, M. Fayez and S.K. Quadri, Kansas State University, Manhattan, KS 66506.

Cysteamine (CSH) has recently been shown to decrease serum prolactin (PRL) and deplete pituitary PRL in the rat. The mechanisms by which CSH produces these effects are not clear. The present study was carried out to determine the effects of morphine sulfate (MS, 5 mg/Kg), Haloperidol (HAL, 0.5 mg/Kg), a dopamine receptor blocker, and 5-hydroxytryptophan (5-HTP, 30 mg/rat), the serotonine precursor, on CSH-induced decrease in plasma prolactin. Male Sprague-Dawley rats were used and blood samples collected from atrial cannulae at 0, 90, 120, 150, 180 and 210 min after CSH treatment. Plasma PRL decreased by more than 50% 90 min after a single injection of CSH (90 mg/Kg, S.C.) and remained at that level during the remaining period of observation. Conversely, and as expected, a single injection of MS or HAL or 5-HTP produced several-fold increases in plasma prolactin. When MS or HAL was injected 90 min after CSH injection they were unable to counter the CSH-induced decreases in plasma prolactin, but a single injection of 5-HTP 90 min after CSH treatment raised plasma prolactin levels by more than 4-fold and countered the CSH-induced decrease in plasma PRL.

These results indicate that CSH-induced inhibition of prolactin release in the rat does not involve opioid or dopaminergic systems but is, at least in part, brought about through serotonergic mechanisms.

19.5

NORADRENERGIC MODULATION OF PINEAL SEROTONIN (5HT) SYNTHESIS AND SECRETION IN VITRO. D.L. Sparks*, J.T.Slevin* and R.F. Walker* (SPON: D.R. Wekstein) Sanders-Brown Research Center on Aging, U. Kentucky, Lexington, KY 40536

The purpose of this study was to determine how NE affects the metabolism and/or secretion of pineal 5HT. Rats were killed by decapitation and their pineals were rapidly removed. The glands were preincubated individually in 0.5ml of nutrient media (DMEM) at 37°C for one hour. After preincubation, the media was replaced with an equal volume of fresh media containing NE (10^{-4}M) and/or tryptophan (10^{-4}M) and incubated for two hours. The process was repeated a second time, collecting the media at each interval and finally the pineal glands themselves for subsequent analysis of 5HT. Incubation with substrate alone did not cause 5HT content of the gland or 5HT levels in the media to increase appreciably. On the other hand addition of NE with substrate caused a significant increase in the media levels of both 5-HT and 5-HIAA. Comparison of 5-HT and 5-HIAA levels in the gland and media showed that intraglandular 5-HT turnover is higher in presence of NE. These findings suggest that in addition to activating the pathway for melatonin synthesis, changes in 5HT synthesis and secretion occur in response to NE stimulation of the pineal gland. The daily release of 5HT may contribute to the "clock" function sometimes attributed to the pineal gland. Supported by NIH AG 02867 (RFW), AG 00084, (DLS) and NS 00732 (JTS).

19.6

SINGLE INJECTIONS OF MELATONIN INDUCE TESTICULAR REGRESSION IN PINEALECTOMIZED HAMSTERS ON SHORT DAYS. Marcia Watson-Whitmyre* and Milton H. Stetson. Univ. of Delaware, Newark, DE 19716

The intact golden hamster exhibits a biphasic diurnal sensitivity to melatonin injections that cause gonadal regression. The pinealectomized (pinx) hamster has been said to lack diurnal sensitivity to melatonin, in that 3 injections given during the dark or the light cause regression. We have found that replacement of the pineal with an injection of melatonin restores sensitivity to evening injections in pinx animals, indicating the importance of the phase of the melatonin signal. We now report that single daily melatonin injections during the early half of the dark phase of a short day (LD 12:12) cause testicular regression in pinx hamsters. Ten weeks of injections given at 1, 2, 3, 4, or 6 h after lights out induced significant regression, as judged by the number of animals with regressed (<2000 mg) testes ($p \ll .01$, Chi-square) or distribution of testes weights within groups ($p \ll .02$, Wilcoxon-Mann-Whitney rank sum). Injections given at other times of the light or dark phase were less effective. We also measured pineal melatonin in intact males housed on the same light cycle; the time of the initial elevation of pineal melatonin corresponds to the latter part of the period of sensitivity to melatonin injections. Our results reinforce the hypothesis that the phase of melatonin elevation is an important endocrine signal for the transduction of short-day information. Supported by NSF Research Grant PCM81-11684.

19.7

SHORT PHOTOPERIOD DEPRESSED SERUM TESTOSTERONE, TESTES AND ACCESSORY ORGAN WEIGHT DURING SEXUAL MATURATION IN PRAIRIE DEER MICE: P. Noden, M. Grizzle*, M. Greene*, and J.M. Whitsett*. N. Carolina State Univ., Raleigh, NC, 27606.

Our objective was to determine if serum testosterone accompanies the delayed sexual maturation induced by short days (<11 hr) in deer mice (Peromyscus maniculatus bairdii). Male deer mice (n=40) were randomly assigned to individual cages; one-half to a 16 hr photoperiod (LD) and one-half to a 6 hr photoperiod (SD). Blood was collected once weekly (3 to 10 wks) from the ophthalmic plexus; anesthesia was Ketamine (13 mg/kg) and Acepromazine (33 mg/kg), intramuscularly. Serum testosterone was quantified by radioimmunoassay. In LD-housed deer mice, testosterone increased linearly from 303±71 pg/ml at 3 wks to 2076±437 pg/ml at 5 wks and 3640 ± 567 pg/ml at 8 wks (P<.01). In SD-housed deer mice, serum testosterone increased with age but was lower (P<.01) than testosterone in LD mice. When testes and accessory organs were collected at 10 wks, testes weight was significantly smaller (P<.01) in SD deer mice (324±11.9 mg vs 195±15.7 mg). Likewise, total sex accessory organ weights were smaller (210±19 mg vs 46±8 mg; P<.01) in SD animals. In conclusion, serum testosterone concentration was depressed by a 6 hr photoperiod. The lower testes and accessory organ weight that accompanied the short photoperiod treatment may be due to depressed testosterone production (supported in part by EPA Cooperative Agreement CR809428010).

19.8

2-BROMO-α-ERGOCRYPTINE (CB154) DECREASED SERUM PROLACTIN AND TESTOSTERONE, FLANK GLAND DIAMETER, TOTAL ACCESSORY SEX GLAND AND TESTICULAR WEIGHT IN PREPUBERTAL MALE GOLDEN HAMSTERS. C. Stroud,* J.M. Whitsett,* and P.F. Noden, N. Carolina State Univ., Raleigh, NC 27606.

The objective was to determine if prolactin is required for testosterone production and the growth of testosterone dependent organs during sexual maturation of the male hamster. Selected parameters were observed at 4 or 5 weeks age after daily administration of CB 154 (500 µg) from day 10 postnatally (n=24). Controls (n=24) received vehicle only. Serum prolactin, quantified by radioimmunoassay, was 0.76±0.12 ng/ml and 0.62±0.04 ng/ml at 4 and 5 weeks respectively in controls. After CB154, prolactin was nondetectable (<0.05 ng/ml; P<.01) at both ages. In addition, serum testosterone was lower (<.05) in CB154 treated animals by 5 weeks of age (1515± 315 pg/ml vs 406±110 pg/ml, P<0.05) as were other parameters: flank gland diameter (4±0.5mm vs 1±0.4mm); testicular weight (710±41mg vs 411±64mg); total accessory gland weight (58±4mg vs 26±2mg). In summary, treatment of prepubertal male hamsters with CB154 depressed not only serum prolactin but also serum testosterone, testicular and total accessory gland weights, and flank gland diameter. These results suggest that prolactin supports testosterone production during sexual maturation and may directly or indirectly support the development of androgen dependent tissues. (EPA Cooperative Agreement CR809428010).

19.9

DISTRIBUTION OF CITRATE AND ASPARTATE IN RAT VENTRAL PROSTATE Renty B. Franklin, L. C. Costello and I. Mason.* University of Maryland at Baltimore, Baltimore, MD 21201

In prostate epithelium citrate is a secretory end-product of metabolism, not a readily oxidized intermediate. These cells show limited citrate oxidation and consequently do not provide a cyclical regenerating source of oxalacetate (OAA). We have proposed that aspartate via aspartate aminotransferase provides the principal 4-carbon source of OAA for citrate production. This is consistent with the observation that rat ventral prostate contains an extraordinarily high level of aspartate in addition to citrate. The distribution of citrate and aspartate was studied in order to determine whether there is compartmentalization of these substrates within the gland. Washout kinetic studies of fragments preloaded with C^{14} and H^3 aspartate as well as endogenous washout were performed. Washout kinetics followed the two-phase kinetics expected of a two-compartment system. There was a rapid phase which represents the washout from gland lumen followed by a slower washout from a cellular compartment. Extrapolation was used for the determination of intracellular concentration. The results indicate that citrate is contained primarily in the luminal compartment and that aspartate is contained in the cellular compartment. Furthermore, the significant difference in washout rate from the slower compartment suggests that efflux of these substrates was not by simple diffusion. (Supported in part by NIH grant HD16193 and AM28015)

19.10

ENDOGENOUS SOURCE AND UTILIZATION OF ASPARTATE BY PROSTATE GLANDULAR EPITHELIAL CELLS. L. Costello, R. B. Franklin and B. Kukoyi*. Univ. of Maryland at Baltimore, Baltimore, MD 21201

In prostate, citrate is an end product of metabolism which is accumulated and is secreted in extraordinarily high levels. We have proposed that aspartate provides the 4-carbon source of oxalacetate which condenses with the 2-carbon acetyl CoA for citrate synthesis. Prostate tissue contains an unusually high endogenous concentration of aspartate (about 3000 nmols/gram). The source of this continual supply of aspartate may be either exogenous uptake from plasma or from endogenous intracellular precursors. We investigated the latter possibility using rat ventral prostate glandular fragments(essentially all epithelial cells). Prostate contains an extremely high level of asparagine (about 1500 nmols/gram). Possibly asparagine could be deaminated to aspartate by asparaginase. However no appreciable level of asparaginase activity was detected in prostate preparations. When prostate cells were incubated in the absence of exogenous substrates, the aspartate and asparagine levels were significantly increased. When we stimulated aspartate utilization by the addition of αKG, the endogenous aspartate level decreased although endogenous asparagine was unchanged. We conclude that asparagine is not a source of aspartate; and possibly both aspartate and asparagine are derived endogenously from protein degradation. (Supported in part by NIH grants HD16193 and AM20815)

19.11

MITOMYCIN C AND ITS EFFECTS ON DAILY SPERM PRODUCTION POTENTIAL (DSP) AND OTHER SPERMATOGENIC PARAMETERS IN CD-1 MICE. J. Fernandez-VanCleve*, B. Salim* and P. M. Zavos* (SPON: S. J. Legan). Univ. Ky., Lexington, KY 40546.

Eighteen CD-1 mice were randomly allocated into three different groups and treated daily for five consecutive days. The treatments (T) were: 1) control, 0.2 ml daily dose of PBS (vehicle), 2) 1.0 mg of mitomycin C (Sigma Co.) per kg of body weight, and 3) 2.0 mg of mitomycin C per kg of body weight. Treatment doses were administered intraperitoneally. All animals were sacrificed 35 days later. Testes and epididymides were excised and caudal epididymal samples were immediately analyzed for sperm count, motility % and progressive motility (grade). Testes were analyzed histologically and DSP measurements were obtained. In T_3 all animals died within the first 19 days of treatment. In the remaining two treatments, mean values for DSP, sperm count per high power field (HPF), percent motility and grade (0-4) were 166.7×10^6 and 26.3×10^6, 44.7 and 12.5, 48% and 3.3%, 3.17 and 0.41 for T_1 and T_2, respectively. Values in all parameters assessed were reduced in T_2(P<.01). Testicular histology indicated a high degree of seminiferous epithelium destruction and increased vacuolization associated with treatment of mitomycin C. The data indicates that mytomycin C causes several pathological changes to spermatogonial cells within the seminiferous tubules and which in turn may induce spermatogenic dysfunctions sensed in all measurements applied in this study.

19.12

SITE OF INSEMINATION AND FERTILIZATION IN SUPEROVULATED COWS. A. Pallares*, P.M. Zavos*, and R.W. Hemken*. (SPON: S.J. Legan). Univ. Ky., Lexington, KY 40546.

Sixteen dairy cows were superovulated with pregnant mare serum gonadotropin (NIH-Bethesda, MD) and were artificially inseminated (AI) 12 hours after onset of heat with a single dose of frozen semen from the same bull. Animals were grouped by AI location site as follows: 1) Right uterine horn (n=4) 2) Left uterine horn (n=3), 3) mid-uterine body (n=3), 4) mid-cervix (n=6). The number of unfertilized ova, retarded and normal embryos were recorded for each horn by flushing at slaughter five to six days after AI. Embryos recovered from the horn where AI was performed (ipsilateral) were pooled and compared to embryos recovered from the opposite horn (contralateral). Embryos from left and right horns were pooled within the remaining treatments. Conception rate (CR) in the ipsilateral horn was significantly higher (P<0.05) than that of the contralateral horn (33 of 38 vs 23 of 37, respectively). Similar CR resulted when AI was performed in the body of the uterus (30 of 43), cervix (33 of 46) and ipsilateral horn. Although no significant differences (P>0.05) were observed, higher CR were found in cows AI in the body of the uterus and cervix than in the contralateral horn. The differences in CR observed among the treatments in this study may be due to alterations in sperm migration imposed by variations in AI location.

20.1

ANGIOTENSIN II (AII)-INDUCED HYPOTHERMIA. Karen M. Wilson* and Melvin J. Fregly, Univ. Florida, Col. Med., Gainesville 32610.

Systemic admin. of AII (100 and 200 µg/kg, s.c.) to the rat induced a hypothermic response characterized within 12 min by a reduction in O_2 cons., vasodilation of the tail and a 1.2° C. fall in colonic temp. (CT). The duration of the response was dose-related. AII (200 µg/kg, s.c.) also induced a hypothermic response which was abolished by pretreatment with captopril (35 mg/kg, i.p.). The interaction of AII with cholinergic and adrenergic pathways which mediate thermoregulatory responses was evaluated. Combined treatment with AII (200 µg/kg, s.c.) and propranolol, a β-adrenergic antagonist (6 mg/kg, i.p.), resulted in a greater depression of CT than was observed with AII alone, but did not affect the increase in tail skin temp. (TST). Admin. of AII in combination with atropine sulfate (6 mg/kg, i.p.), which crosses the blood brain barrier (BBB), significantly reduced the extent of fall in CT without affecting the inc. in TST. Combined treatment of AII and atropine methyl nitrate (3.25 mg/kg, i.p.) which does not cross the BBB, failed to affect the hypothermic responses. The hypothermic responses induced by admin. of AII may be mediated via a central cholinergic pathway, and possibly influenced by an adrenergic component. The inability of both adrenergic and cholinergic blockers to affect TST to admin. of AII suggests that the component of the AII response affecting mechanisms subserving heat production can be blocked independently of those subserving heat loss. (Supported by grant AM 31837 from NIH).

20.2

INDIRECT METHODS TO DETECT OVULATION ARE INADEQUATE FOR STUDIES ON ENVIRONMENTAL STRESS. A. J. Carpenter* and S. A. Nunneley. USAF Sch Aerospace Med, Brooks AFB, TX 78235.

Studies of women's responses to environmental stress often address possible influences of the menstrual cycle. Two methods are often used to partition the cycle into follicular and luteal phases: detection of a postovulatory rise in basal temperature (T_{bas}) or arbitrary division by number of days elapsed since menses onset. We evaluated these methods versus hormone assays for 2 to 3 cycles in 8 informed women volunteers. Serum was assayed for estradiol (E_2), progesterone (Pg), LH, and FSH. Subjects recorded T_{bas} (± .1° F) daily. Ovulation was confirmed by an LH peak followed by a rise in Pg. We defined the follicular phase as menses onset to the day preceding ovulation, and the luteal phase as ovulation to the day preceding the next menses. Cyclic changes in hormone concentration and T_{bas} varied widely both within and between subjects. Postovulatory rises in T_{bas} appeared in 10 of 17 ovulatory cycles, and the time to detect the T_{bas} change relative to ovulation was -1 to +5 days. Lengths of the 17 cycles were 25-39 days ($\bar{x}$=30), and most of the variability resided in the follicular phase (11-25 days). Thus, the indirect methods often used were poor indices of ovulation or phase length. We conclude that studies of interactions between the menstrual cycle and environmental stress responses must include direct evaluation of hormone status. Which hormones should be observed must be determined by the hypothesis being tested.

20.3

CONTROL OF SWEAT RATE IN THE PATAS MONKEY. Mallard D. Owen* and Carl V. Gisolfi. The University of Iowa, Iowa City, IA. 52242

In 2 male (10-13 kg) patas monkeys (Erythrocebus patas), 3 pairs of stainless steel thermodes were implanted bilaterally to permit control of preoptic/anterior hypothalamic temperature (T_{hypo}). Animals were housed at an ambient temperature (T_a) of 32 ± 2°C for 3 months prior to study. Experiments were performed with animals restrained in primate chairs and instrumented to yield the following information: T_{hypo}, colonic temperature (T_c), mean skin temperature ($\bar{T}_s$), chest sweat rate (SR), and heart rate (HR). To alter T_{hypo}, 4 thermodes were perfused with water from a temperature-controlled bath. T_{hypo} was monitored using a thermocouple inserted to the tip of a non-perfused thermode. SR was measured using resistance hygrometry. The experimental procedure consisted of allowing the animal to equilibrate to a selected T_a and then changing T_{hypo} in a stepwise or ramp fashion. Provided $\bar{T}_s$ was sufficiently high, increasing or decreasing T_{hypo}, with no significant change in T_c or $\bar{T}_s$, elevated or reduced SR, respectively. Using either perfusion protocol, increasing T_{hypo} between 37 and 41°C increased SR to values of 0.3 $mg \cdot cm^{-2} \cdot min^{-1}$. Decreasing $\bar{T}_s$ shifted the T_{hypo}-SR relationship to the right. Activity-induced changes in HR, when T_{hypo} was constant, caused fluctuations in ongoing sweating that closely tracked the HR response. We conclude that SR in the patas monkey is controlled by both peripheral and central thermal inputs and non-thermal factors.

20.4

PERIPHERAL CHANGES IN REGIONAL SWEATING RESPONSES TO EXERCISE IN HYPOBARIC ENVIRONMENTS. M.A. Kolka, L.A. Stephenson, P.B. Rock*, and R.R. Gonzalez. US Army Research Institute of Environmental Medicine, Natick, MA 01760

Regional sweating to body temperature rise ($\dot{m}_s$:T_{es}) affected by hypobaric hypoxia was studied. Four men and four women (follicular phase of menstrual cycle) exercised at 40 and 60% of their altitude specific peak aerobic power at sea level (770 torr), 2596m (552 torr), and 4575m (428 torr) in 20°C or 30°C for 35 minutes. T_{es} and $\dot{m}_s$ at the chest (C), arm (A) and thigh (T) were measured continuously from dew point sensors attached to the skin. No gender differences were found in either the sensitivity (slope) or the threshold of the $\dot{m}_s$:T_{es} for any site during any permutation of exercise intensity, altitude or environmental temperature. Mean slopes (n=8) for the three regional sites during the exercise-temperature treatments decreased with increasing altitude and are shown below for sea level and high altitude.

	Sea Level			4575m		
Treatment	C	A	T	C	A	T
20°/60%	0.87	1.08	0.98	0.58	0.59	0.81
30°/40%	1.27	1.48	2.20	0.67	0.96	0.93
30°/60%	1.04	1.84	1.31	0.60	0.90	0.95

In all experimental conditions, the A threshold (36.7°C) for the initiation of sweating was higher than C (36.5°C) or T (36.5°C). Our data indicate that there are peripheral components active in the regional $\dot{m}_s$:T_{es} relationship that occur in hypobaric hypoxia, suggesting either active cooling as a response to higher skin diffusion, or an hypoxic influence at the individual sweat gland.

20.5

THE EFFECT OF CUTANEOUS DENERVATION OF THE FACE AND TRUNK ON THERMOREGULATORY RESPONSES TO COLD IN RATS. Martha E. Heath. Physiolgical Research Laboratory, UCSD, La Jolla, CA 92093.

The ability to thermoregulate in a cool environment was assessed by measuring rate of heat production and body temperatures in a 25 C environment and during slow (20 min: n=2) and rapid (5 min: n=2) reductions of ambient temperature (T_a) to 15 C. Measurements were made before and during the two weeks after cutaneous denervation of the trunk and face. Also, the resting metabolic rate was determined for a range of T_a before and 7-10 days after cutaneous denervation (n=8). Cutaneous denervation was achieved by sectioning spinal and cranial nerves at the muscle and skin interface. Sterile surgical technique was used in fully anesthetized rats. O_2 consumption was measured in an open circuit system. Rectal temperature and skin temperature on the back, ear and tail were monitored with thermocouples. Rats regulated body temperature well even after the cutaneous nerves of the trunk and face were sectioned, but the metabolic rate was higher in the denervated condition in both T_a. The minimal resting metabolic rates did not differ in the two conditions (4.9 W/kg), but the lower critical temperature was elevated from 26.8 to 28.9 C and the rate of rise in metabolic rate per C drop in T_a was also higher after denervation (-.54) than before (-.44). It is concluded that eliminating most of the input from cutaneous thermoreceptors doesn't substantially impair a rat's ability to regulate body temperature although insulation is reduced and heat production must increase to offset additional heat loss. (5 R01 HL29006-02)

20.6

THE ONSET OF HYPOTHERMIA IN SUCKLING FATTY (fa/fa) ZUCKER RATS. Ingrid Schmidt*, Randy Kaul* and Harry J. Carlisle. Dept. of Psychology, UCSB, Santa Barbara, CA 93106, USA, and Max-Planck-/W.G. Kerckhoff-Institut, D-6350 Bad Nauheim, FRG.

To determine the onset of a reduced energy expenditure in fa/fa rats we measured core temperature (Tc) daily during the first two weeks in huddling pups under rearing conditions (Ta=25°C). Pups were identified retrospectively as being of lean (Fa/-, N=18) or fatty (fa/fa, N=6) genotype. Tc was measured 2 or 3 times during each of 2-5 sessions evenly spaced throughout the light phase (0700-1900). Measurements were started when all pups had been huddled together in the absence of the dam for at least 15 min. Insertion depth of the 1 mm diameter thermocouple probe was increased from 1.8 cm in 1-day-old pups to 3.0 cm in 14-day-old pups. Daily mean body temperature (Tc) of Fa/- pups varied between 35.2±0.2 (±SE) and 35.5±0.1°C from day 2 through 9, and then increased to 36.0±0.1°C by day 14. Tc of fa/fa pups was only 0.08±0.14°C below that of their lean littermates on day 1 and 0.05±0.05°C below it on day 5. On day 6 this difference increased to 0.47±0.14°C, significantly different from 0 ($p<0.05$). Tc of fa/fa pups averaged 0.66±0.06°C below that of their Fa/- littermates from day 7 through 10 and 0.94±0.08°C during the next four days. The abrupt onset of hypothermia suggests a critical event in the etiology of genetic obesity occurring on day 6. (Supported by: Max Kade Foundation and AM32984 from NIADDKD)

20.7

FATTY AND LEAN ZUCKER RATS DEFEND A SIMILAR BODY TEMPERATURE WITH MATURITY. R. Kaul*, I. Schmidt* and H. J. Carlisle. Dept. of Psychology, UCSB, Santa Barbara, Ca. 93106, USA and Max-Planck-/W.G. Kerckhoff-Institut, D-6350 Bad Nauheim, FRG.

Fatty (fa/fa) Zucker rats are defective in their capacity for non-shivering thermogenesis (NST). To explore for other thermoregulatory differences between fatty and lean (Fa/-) rats, we have analyzed defense of core temperature (Tc,°C) at different ages in littermates reared in group cages at 25°C. To minimize effects of differences in spontaneous activity, Tc was recorded continuously for at least 1.5 h in individuals lightly restrained in tubular cages. Rectal probes were inserted 3 cm in pups and 6 cm in adults. In 16-day-old pups isolated at 25°C Tc after 1.5 h was significantly lower ($P<0.05$) in fatty pups: Tc(fa/fa)=34.3±0.3 (±SE), N=6 and Tc(Fa/-)=36.5±0.1, N=20. In 24-day-old pups at 25°C, however, Tc was not different between genotypes: Tc(fa/fa)=37.6±0.1, N=6 and Tc(Fa/-)=37.7±0.1, N=14. But during 1.5 h at 5°C on the next day, Tc still fell significantly lower in fatty pups: Tc(fa/fa)=32.2±1.3, N=5 and Tc(Fa/-)=35.9±0.9, N=12 . In adults (3-6 months) Tc no longer differed significantly between genotypes: even after 3 h at 5°C Tc(fa/fa)=36.8±0.2, N=11 and Tc(Fa/-)=36.2±0.4, N=17. Under conditions that minimize NST (acute cold exposure of non-acclimated adults) fa/fa rats defended the same body temperature as their Fa/- littermates. (Supported by: AM32984 from NIADDKD and Max Kade Foundation)

20.8

EFFECT IN THE CAT OF α-MELANOCYTE STIMULATING HORMONE ON CENTRALLY-INDUCED ENDOTOXIN FEVER. Amir H. Rezvani, D. M. Denbow and R. D. Myers. University of North Carolina School of Medicine, Chapel Hill, NC 27514

α-MSH has been shown to attenuate fever in rabbits. The present experiments were carried out in order to determine whether the response to ICV α-MSH exhibits a species continuity, and to examine the interaction between α-MSH and norepinephrine (NE). While colonic temperature was recorded an ICV infusion (300 µl) was given of CSF control vehicle, 1:100 dilution of E. coli endotoxin, 50 mM Ca^{++} ions, 100 µg NE or α-MSH in seven doses from 50 ng to 5.0 µg. Whereas E. coli induced an intense and prolonged fever of rapid onset, α-MSH infused similarly was essentially without effect. However, NE always lowered the deep body temperature of the normothermic cat. Each of the ICV doses of α-MSH, or a mixture of E. coli with α-MSH, failed to alter the characteristics of the endotoxin fever produced in the cat. Either excess Ca^{++} given ICV or an antipyretic drug administered systemically during the fever effectively reduced the cat's elevated body temperature. Different ICV doses of α-MSH prior to NE injection or combined with NE attenuated the hypothermic effect of NE. These results indicate that in the feline species, α-MSH serves neither as a mediator of heat loss pathways in the normothermic cat nor as an antipyretic agent in the febrile animal. However, these data suggest a neuromodulatory role for this neuropeptide.

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20.9

RESPIRATORY HEAT LOSS AT ALTITUDE: EFFECT OF $\dot{V}O_2$ PEAK. R.R. Gonzalez, L.A. Stephenson, W.L. Holden* and M.A. Kolka. US Army Res. Inst. Environ. Med., Natick, MA 01760.

At standard atmospheric pressure (P_b = 760 torr) latent respiratory heat loss (E_{res}, W/m^2) is a function of metabolic rate (M). Since hyperventilation is a prominent immediate response in acute high altitude exposure (AHA) and $\dot{V}_E$ increases with exercise, the presence of or degree of water vapor loss in the alveoli is a critical property as P_b falls. We examined the relationships between E_{res}:M, E_{res}:$\dot{V}O_2$ as a function of the gradient in (P_s,T_{es}) and water vapor (P_w) during exercise to exhaustion at sea level (SL) (P_b = 770 torr) and AHA at 4575m (P_b = 428 torr) at T_a = 24°C and T_{dp} = 10°C. Four, fit, non-smokers (2 males, 2 females) after warm-up exercised to their $\dot{V}O_2$ peak on a modified cycle ergometer. Continuous T_{dp} (automatic dewpoint sensors) and air temperatures were recorded on separated inspired and expired air through a heated (38°C) 2-way respiratory valve; absolute humidity ratio was measured. T_{es}, $\dot{V}O_2$,$\dot{V}_E$ (BTPS & STPD) were continuously recorded. For each subject, E_{res} at SL followed predicted equations for M and $\dot{V}O_2 \leq$ 360 W/m^2 and 2.3 L/min, but deviated at high M and AHA. The slopes in E_{res} :M, E_{res} :$\dot{V}O_2$ and E_{res}:$\dot{V}_E$ (STPD) were higher ($P < 0.01$) at AHA compared to SL, but predicted by eq. E_{res} = 0.52 ($\dot{V}_E$, BTPS) + 4.48 (r^2=0.97); however, for SL and AHA at $\bar{T}_b$ = 37°C, $E_{res} = 0.0175 \cdot \dot{V}_E$ (44-P_w). Consistent with a hyperventilatory response, our study shows that the respiratory tract plays an increasing role in E_{res} with exercise in a hypobaric environment.

20.10

CHRONIC CONSUMPTION OF A LOW-SODIUM DIET IN RATS: RESPONSES TO HEAT EXPOSURE. R.P. Francesconi and R.W. Hubbard. US Army Res. Inst. Environ. Med., Natick, MA 01760

To determine the effects of a low sodium (Na^+) diet on the responses to severe heat stress (35.5°C), immature ($\bar{X}$ = 150.4g) male rats (n=21) were fed a low-Na^+ diet for 71 days. Weight gain and food consumption were significantly ($p < .001$) reduced in the low-Na^+ group while water consumption was unaffected. Circulating Na^+ levels were unaffected by Na^+ restriction while both potassium (K^+) and hematocrit levels were significantly ($p < .001$) increased. After 24h heat exposure circulating Na^+ levels decreased significantly ($p < .001$) in the low Na^+ group. Potassium levels increased ($p < .01$) in the control group after 6h of heat, but did not attain levels of the low Na^+ group. While plasma renin activity (PRA) was not increased by the low-Na^+ diet or by heat exposure in the control group, heat stress in the low-Na^+ group did elicit significant ($p < .005$) increments in PRA after 24h. Alternatively, plasma aldosterone levels were significantly ($p < .001$) elevated by both the low-Na^+ diet and heat stress. Survivability was also affected by the low Na^+ diet since after 24 h of heat exposure 23/25 control rats survived while in the low-Na^+ group only 9/21 remained. This high incidence of mortality may be associated with a thermoregulatory deficit in this group since the mean T_{re} of surviving controls at 24 h was 39.7 ± .1°C while that of the comparable low-Na^+ group was 40.8 ± .2°C. We concluded from these studies that the low-Na^+ diet had severe effects on hematological, endocrinological, and thermoregulatory variables as well as thermal sensitivity to prolonged heat exposure.

20.11

EXPANSION OF TOTAL BODY WATER FOLLOWING HEAT ACCLIMATION. V.A. Convertino and C.R. Kirby*. University of Arizona, Tucson, AZ 85721

Ten male subjects (24 ± 2 yr) performed cycle exercise at 45% VO_2 max in the heat (40 °C DBT, 45% rh) for 2 hr/day for 10 consecutive days to determine if increased plasma volume (PV) that accompanies exercise and heat acclimation (EHA) is associated with total body water (TBW) expansion. PV (T-1824) and TBW (ethanol dilution) were measured before and after EHA. Total body fluid balance was determined from 24-hr water intake and urine volumes. Resting plasma and 24-hr urine were measured for sodium (Na), potassium (K), osmolality (Osm), protein, creatinine (Cr), and plasma aldosterone (PA), and renal clearances were calculated. Following EHA, PV increased by 376 ml (+12.4%, $P < .05$) with a concomitant TBW expansion of 2.58 L (+5.7%, $P < .05$). Despite a mean 24-hr fluid loss of 2792 ml from sweat during daily heat exposure, a net gain of 269 ml/day resulted from an increase in 24-hr water intake from 1892 ± 105 to 4716 ± 279 ml ($P < .05$) and a decrease in 24-hr urine volume from 1235 ± 91 to 998 ± 88 ml ($P < .05$). Following EHA, a reduction in 24-hr Na clearance from 0.72 ± .08 to 0.34 ± .06 ml/min ($P < .05$) was associated with no change in resting PA while 24-hr free water clearance increased from -1.43 ± .20 to -0.94 ± .16 ml/min ($P < .05$). These data suggest that TBW expansion occurs with EHA as a result of greater renal Na and water retention. This mechanism may reflect an increased sensitivity to circulating aldosterone.

20.12

UNUSUAL BLOOD COAGULATION IN A HIBERNATOR, THE DEER MOUSE (P.leucopus). G. Edgar Folk, Jr., Whyte Owen*, and Daniel Smith*. Departments of Pathology, Physiology and Biophysics. The University of Iowa, Iowa City, Iowa 52242.

Blood from albino mice clots in glass tubes (Lee-White test) in approximately two minutes. In contrast, blood from deer mice collected on the Alcan Highway did not clot at all. Blood from winter and summer deer mice from Iowa, and summer deer mice from Connecticut, Georgia and Texas (N=84) either did not clot or formed a transient clot which became liquid within 1-5 min; one sample from Texas clotted permanently. A small (< 1/10 of specimen vol.) clump remained in most specimens. Blood collected into EDTA (5 mM final conc.) and then clotted with bovine thrombin (10 µg/ml final conc.) gelled within 10 sec but then liquified within 5 min (37°), and had no residual clumps. The mechanism of the phenomenon is unknown, but may be an exceptionally enhanced spontaneous clot lysis.

21.1

LEFT VENTRICULAR FLOW DISTRIBUTION AFTER 2HR REGIONAL ISCHEMIA AND 60 MINUTES REPERFUSION IN THE EMPTY BEATING ISOLATED PIG HEART. William Dobbs, R. Jones* and R.M. Engelman*University of Connecticut Health Center,Farmington,CT 06032. Occlusion of the left anterior descending coronary artery of the isolated empty beating pig heart(n=3) reduced flow from an average control value of 3.4(HCT=15) to 0.21 and 0.14ml/gmin in the ischemic subepicardium and subendocardium respectively. After 2 hr occlusion and 60 minutes reperfusion of the formerly ischemic region flow was 2.36 and 0.86 ml/gmin in the subepicardium and subendocardium respectively. Flow in the nonischemic region was 2.72 ml/gmin. Thus, flow recovery in the ischemic reperfused subepicardium was about 2.5 times greater than that to the subendocardium. Occlusion reduced the subendo/subepi ratio from a control value of 1.39 to 0.53. This relationship persisted throughout reperfusion since the respective values were 1.20 and 0.36 after 60 minutes reperfusion. Prolonged perfusion elevated coronary resistance by a factor of 2 in two of three hearts. The relative vulnerability of the subendocardium to reperfusion injury in this model of regional myocardial ischemia may be due to tissue factors, either cellular or microvascular since the hemodynamic factors which influence subendocardial perfusion such as end diastolic pressure and pulsatile aortic pressure were artificially controlled or minimized.

21.2

RELATION OF SYSTOLIC SUBEPICARDIAL PRESSURE TO SYSTOLIC CORONARY BLOOD FLOW. H.N. Sabbah, M. Marzilli*, Z.O. Liu* and P.D. Stein. Henry Ford Hospital, Detroit, MI 48202

A systolic intramyocardial pressure in the subepicardium (EPI) of the left ventricle which is less than systolic aortic pressure (AP) has been proposed as an explanation for the systolic component of coronary blood flow (SCBF). To determine whether augmentation of systolic EPI pressure relative to systolic AP influences the magnitude of SCBF, studies were performed in 7 open-chest dogs in which the left anterior descending coronary artery was cannulated and perfused from the left carotid artery. EPI pressure was measured with a #3F micromanometer inserted directly into the EPI of the perfused region. To augment EPI systolic pressure, an intracoronary injection of 1 ug of isoproterenol was made before and after local maximal vasodilatation with adenosine. The results are shown in the table as mean ± SEM. (*P<.01; **P<.001 relative to control)

	Control			Isoproterenol		
Coronary Bed	AP (mmHg)	EPI (mmHg)	SCBF (ml/min)	AP (mmHg)	EPI (mmHg)	SCBF (ml/min)
Regulated	168±5	127±5	18±4	162±5	222±12	-2+4*
Vasodilated	158±5	122±5	103±6	153±5	204±16	38±11**

In both the regulated and maximally vasodilated bed, mean SCBF decreased as systolic EPI pressure increased above systolic AP. This observation indicates that coronary extravascular compression in the EPI is important in the regulation of SCBF.

21.3

EFFECTS OF EXERCISE TRAINING ON RESTING CORONARY VASCULAR RESISTANCE AND MYOCARDIAL ADENOSINE IN THE RAT. E.L. Warner*, D.D. Fletcher*, and J.E. McKenzie. Dept. of Physiology, Uniformed Services University, Bethesda, MD 20814

Previous studies in the anesthetized, open-chest rat have shown increased myocardial adenosine (ADO) and catecholamine contents without a change in coronary vascular resistance(CVR) after a 10-week swimming program. To examine the effects of a running program on CVR and ADO, male Sprague-Dawley rats(200g) were randomly divided into sedentary and running groups. Running rats were exercised 5 days/wk for 8 weeks on a rodent treadmill at gradually increasing workloads up to a rate of 27 m/min, for 50 min, at an 8% grade. After 8 weeks, all rats were anesthetized with NaPentobarbital and hearts were exposed by sternotomy. Coronary blood flow was measured by a left atrial injection of 15μ radiolabelled microspheres. Hearts were excised in situ with nitrogen-cooled tongs. ADO was measured spectrophotometrically. There was no change in CVR ($p<.05$) in the running group (.41±.07mmHg·ml·min^{-1},n=12) relative to the sedentary group (.26±.03mmHg·ml·min^{-1},n=14). ADO was significantly elevated ($p<.05$) in the running group (11.5±2nmoles/g) as compared to the sedentary group(5.2±.7nmoles/g). As in the swimming program, running caused an increase in ADO without a decrease in CVR. In exercised-trained rats ADO production may be enhanced to maintain the same CVR, ADO storage may be increased to allow greater vasodilator reserve during exercise, or receptor sensitivity to ADO may be reduced due to repeated bouts of exercise. (Supported by USUHS RO7682)

21.4

CHARACTERIZATION OF THE CORONARY VASCULAR RESPONSE TO HISTAMINE IN RABBIT HEARTS USING CIMETIDINE AND THEOPHYLLINE. Jack T. Saari, Univ. of N. Dakota, Grand Forks, ND 58202.

Successive applications of histamine in the isolated, perfused rabbit heart revealed a transient constriction of coronary vasculature. The mechanism of this vasoconstriction, in particular its tachyphylactic nature, was the subject of this study. Diphenhydramine, a histamine H_1-receptor antagonist, perfused during one of the applications of histamine blocked the vasoconstriction, confirming an H_1-receptor mediated response. Cimetidine, a histamine H_2-receptor antagonist, perfused during one of the applications of histamine enhanced the vasoconstriction, indicating that H_2-receptors mediate an inhibition of vasoconstriction. Cimetidine perfused during all applications of histamine reduced and in some cases eliminated the apparent tachyphylaxis, implying that the waning vasoconstrictor response normally seen with histamine was due to a gradually increasing H_2-receptor mediated inhibition. Cyclic AMP perfused during one of the applications of histamine inhibited the vasoconstriction, suggesting a possible chemical mediator of the H_2-receptor mediated inhibition. Theophylline (a phosphodiesterase inhibitor) perfused during one of the applications of histamine inhibited the vasoconstriction, further evidence for a cyclic AMP-mediated mechanism of H_2-receptor activity.

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21.5

CATECHOLAMINES INACTIVATE ENDOTHELIAL RELAXING FACTOR IN CANINE CORONARY ARTERIES. G.M. Rubanyi* and P.M. Vanhoutte, Dept. Physiol., Mayo Clinic, Rochester, MN 55905.

The presence of the endothelium augments the contractions evoked by norepinephrine in several arteries. The present study was designed to investigate the interactions between catecholamines and endothelial cells. Rings of isolated canine coronary arteries, without endothelium, were suspended for isometric tension recording and superfused with physiological salt solution (37°C). The superfusate was passed through a segment of femoral artery prior to reaching the coronary ring. Acetylcholine, added to the superfusate before it reached the femoral artery, induced relaxation of constricted (prostaglandin $F_{2\alpha}$), atropinized coronary arteries only if the femoral artery contained endothelium. This demonstrates that acetylcholine acts by releasing endothelial relaxing factor(s). The relaxation induced by acetylcholine was reversed by adding norepinephrine or epinephrine to the superfusate. This reversal was not affected by alpha- and beta-adrenoceptor blocking agents. If added to the superfusate between the femoral and coronary arteries the catecholamines still reversed the relaxations caused by acetylcholine. Thus, the catecholamines interact directly with endothelial relaxing factor(s), rather than interfering with its endothelial production or its smooth muscle action. (Supported in part by grant HL 31183.)

21.6

ACIDOSIS AND ACTIVE CA TRANSPORT BY PORCINE CORONARY ARTERY SUBCELLULAR FRACTIONS. S. Samson* and A.K. Grover. Neurosciences Dept., McMaster University, Hamilton, Ontario, Canada, L8N 3Z5.

Pig coronary artery subcellular fractions were isolated as described earlier (Fed. Proc. 43: 429), and the effects of Ca^{2+} and pH on their ATP-dependent Ca-uptake at 5 uM Ca^{2+}, and 500 mM free ATP and Mg^{2+} was examined. The oxalate independent azide insensitive Ca-uptake by the plasma membrane enriched fraction (PM), the oxalate-independent azide sensitive Ca-uptake by the mitochondrial-enriched fraction (MIT), and the oxalate-stimulated Ca-uptake by the endoplasmic reticulum-enriched fraction (ER) were examined. The Ca-uptake by the PM fraction (no oxalate) was linear only for 1 min while the ER (oxalate-stimulated) Ca-uptake was linear for > 30 min. The effect of pH on the Ca-uptake by PM was as follows: 6.8 = 7.2 > 6.4 >> 7.6. Thus the PM Ca-uptake was optimal under the conditions of acidosis. $K_{0.5}$ for Ca^{2+} for the PM and the ER Ca-uptake were both 0.5-0.6 uM, although the Ca-uptake by ER showed a much larger positive - co-operativity to Ca^{2+} (Hill Coefficent = 2.5) than the uptake by PM (Hill Coefficient = 1.3). The data on the Ca-uptake by the PM, ER and MIT will be compared to address the roles of the various Ca-transport mechanisms in the contractility of the coronary artery in normal and acidosis conditions.

This work was supported by the Ontario Heart Foundation.

21.7

CORONARY ARTERY VASOCONSTRICTION INDUCED BY AN ENDOTHELIAL CELL DERIVED PROTEIN. K.M. Agricola*, M.J. Gallaher*, G. Rubanyi*, R.J. Paul and R.F. Highsmith, Dept. of Physiology & Biophysics, Univ. of Cincinnati, Cincinnati, OH 45267

We have directly evaluated the vasoactive effects of bovine aortic endothelial cell (EC) products on isolated rings of the left anterior descending coronary artery (LAD). EC-conditioned culture media (CM) elicited a significant vasoconstriction in porcine, bovine and canine LAD. After a 0.5 to 5 min latency, maximal tension was usually obtained within 15 min and a substantial tonic component to the contractile response was evident. Increasing volumes of CM in the muscle chamber resulted in progressive increments in isometric tension while control, non-conditioned CM had a negligible effect. The vasoconstrictor is specifically localized to the EC, for conditioned media from control cultures of fibroblasts or vascular smooth muscle cells also had no effect on LAD tone. The EC-CM-induced contraction did not require an intact LAD-endothelium. The vasoconstriction required extracellular Ca^{2+} and was unaffected by cyclooxygenase or lipoxygenase inhibitors or by antagonists to the β-adrenergic, serotonergic, histaminergic or cholinergic receptor systems. Treatment of the EC-CM with either Na dodecyl SO_4, trypsin, alkali or acid hydrolysis completely abolished the vasoconstrictive effect. HPLC, chromatography and calibrated gel filtration indicate that the isolated vasoconstrictor is a polypeptide of Mr=8500 ± 1500 and pI=5.2. The regulation of this molecule could be of major significance in the pathophysiology of hypertension and coronary artery vasospasm. (Supported by NIH and AHA)

21.8

ADENOSINE CONCENTRATIONS IN CANINE CARDIAC LYMPH, CORONARY SINUS PLASMA AND MYOCARDIUM. Jack E. McKenzie, Sharon A. Segal, Booker T. Swindall*, Coleen A. Troy*, and Francis J. Haddy. Department of Physiology, Uniformed Services University of the Health Sciences, Bethesda, MD 20814

To evaluate adenosine production by the canine myocardium, adenosine concentrations (ADO) were measured in cardiac lymph, arterial and coronary sinus plasma, and myocardial tissue. Pure cardiac lymph was obtained by isolating and cannulating the main cardiac lymph vessel within the pericardium, proximal to the pretracheal lymph node. Animals (n=6) were administered a priming dose of Krebs solution (1 L) i.v. Lymph flow was sustained with a 5.3 ml/min infusion. Lymph was collected into ice cold perchloric acid. Blood was mixed with ice cold dipyridamole and centrifuged immediately. Tissue samples were obtained with a nitrogen cooled drill and freeze clamped in less than 1 second. All samples were deproteinated with 1N perchloric acid, neutralized with KOH, and analyzed with high pressure liquid chromatography. Cardiac lymph ADO was 0.297±0.005 μM and cardiac lymph adenosine output was 9.8±0.3 pmoles/min. Coronary sinus ADO (0.250±0.006 μM) minus arterial ADO (0.169±0.006 μM) equaled 0.080±0.005 μM. Myocardial ADO was 2.5±0.2 μM. There was a positive correlation between V-A ADO and cardiac lymph adenosine ($r=0.95$, $P<0.05$) and between myocardial adenosine and cardiac lymph adenosine ($r=0.82$, $P<0.05$). These data demonstrate relationships between adenosine measurements in cardiac lymph, V-A difference, and myocardial tissue. Supported by HL29709 and RO7682.

21.9

THE EFFECTS OF RIGHT STELLECTOMY AND ADRENERGIC BLOCKADE ON RIGHT CORONARY BLOOD FLOW. George E. Billman. Department of Physiology, Ohio State Univ., Columbus, OH. 43210

Several studies have established that neural factors can significantly effect left coronary blood flow (CBF). Since metabolic demand and mechanical compression are lower for the right ventricle, neural activation may contribute more to the regulation of right CBF. Using chronically instrumented dogs (n=7), right CBF and right coronary vascular resistance (CVR) were determined before and during cardiac pacing in each of the following conditions: Control (C), metroprolol (M 1 mg/Kg), prazosin (P, 0.5 mg/kg), phentolamine (Ph, 1 mg/kg) and one week after right stellectomy (RSGx). Right CBF increased and right CVR decreased for every heart rate after alpha blockade (for both P and Ph), and RSGx while the reverse occurred after M. The CVR results (mmHg/ml/min) are presented below ($\bar{X}$ ± SE, **p <0.01 from C)

	Control HR	Paced HR 180 bpm
C	4.4 ± 0.2	3.4 ± 0.2**
M	5.2 ± 0.3**	4.2 ± 0.3
P	3.4 ± 0.2**	2.9 ± 0.1**
Ph	3.3 ± 0.3**	2.9 ± 0.2**
RSGx	2.9 ± 0.2**	2.4 ± 0.2**

These data suggest that neural factors (which probably originate or pass through the right stellate ganglion) contribute significantly to the regulation of right CBF. (Supported by a grant from Am. Heart Assoc. and NIH grant HL30262).

21.10

NEUROGENIC CORONARY CONTRACTIONS DUE TO ACCUMULATION BY ADRENERGIC NERVES OF 5-HYDROXYTRYPTAMINE RELEASED FROM PLATELETS. Richard A. Cohen. Boston University Medical Center, Boston, MA 02118

The purpose of this study was to determine if 5-hydroxytryptamine released from aggregating platelets could serve as a false neurotransmitter in coronary adrenergic nerves. Isometric tension was recorded in rings of canine left circumflex artery suspended in organ chambers. In control rings contracted with prostaglandin $F_{2\alpha}$, transmural electrical field stimulation caused frequency-dependent beta-adrenergic relaxations. Prior exposure of the rings to aggregating platelets (70,000/μl) or 5-hydroxytryptamine (10^{-6}M) for 2 hours resulted in contractions in response to electrical stimulation. The neurogenic contractions resulting from exposure to platelets and 5-hydroxytryptamine were blocked by cyproheptadine or ketanserin, and were also prevented by blocking neuronal uptake with cocaine prior to exposure. Accumulation of radiolabeled 5-hydroxytryptamine by coronary arteries was inhibited by cocaine or by denervation with 6-hydroxydopamine: release of the labeled amine by electrical stimulation was blocked by tetrodotoxin. Thus, 5-hydroxytryptamine released from aggregating platelets can be accumulated by adrenergic nerves and serve as a false neurotransmitter. Serotonergic contractions due to sympathetic nerve activity could contribute to coronary vasospasm at sites where platelets have aggregated. (Supported by HL 31607.)

CONTROL OF BREATHING III

22.1

DOES COPD ALTER THE RELATIONSHIPS AMONG VENTILATION, INSPIRATORY MUSCLE ACTIVITY AND RATING OF PERCEIVED DYSPNEA (RPD) DURING GRADED TREADMILL EXERCISE (GXT)? P. Weiser, F. Arlinghaus, J. Gillen and S. Levine. VA Medical Center and Medical College of Pennsylvania, Philadelphia, PA. 19104.

To answer the above-noted question, we studied 6 COPD patients (Ps) and 4 age-matched normal subjects (Ns) during a 12 stage (ST) modified Balke GXT. End-exercise (EE) results for ST, oxygen uptake in ml/min/kg ($\dot{V}O_2$), ventilation in liters/min ($\dot{V}E$), inspiratory muscle effort (peak inspiratory esophageal pressure divided by maximum corrected inspiratory pressure x 100 = % MIPc), inspiratory muscle EMG activity (sum of % maximum diaphragmatic, intercostal and sternomastoid activity ÷ 3 = % EMGsum) and Borg category-ratio RPD scale score are shown in the following table:

	ST	$\dot{V}O_2$	$\dot{V}E$	%MIPc	%EMGsum	RPD
Ps(n=6)	8±1	14±3	39±13	45±15	48±2	10±1
Ns(n=4)	12±0	24±4	75±15	24±4	25±9	5±1

The increase in RPD was greater in Ps than in Ns for every increase in %EE $\dot{V}E$. However, Ps and Ns exhibited high correlations ($r>.98$) between RPD and both %MIPc and %EMGsum. Moreover, the relationship between RPD and these indices of inspiratory muscle activity (IMA) were similar in Ps and Ns, although RPD and IMA extended to higher values in the Ps group. We conclude that COPD does not alter the relationship between RPD and IMA. The greater RPD-%EE $\dot{V}E$ in Ps may be due to the fact that Ps require greater increments in IMA than Ns to achieve the same increment in %EE $\dot{V}E$.

22.2

DOES VENTILATORY MUSCLE FATIGUE (VMF) LIMIT CONSTANT LOAD TREADMILL EXERCISE (CLTX) IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)? S. Levine, M. Giller, R. Rossi, P. Barnard and P. Weiser. VA Medical Center and Medical College of Pennsylvania, Philadelphia, PA. 19104.

To assess the possibility that VMF limits CLTX, we studied 6 male patients with COPD (Ps). Ps were 65±2 (mean ± SEM) years, $FEV_{1.0}$ was 1.0±.1 liters and $FEV_{1.0}$/FVC was 44±3%; peak $\dot{V}O_2$ of our Ps on a modified Balke graded treadmill exercise test was 16±1 ml/min/kg. In the present study, our Ps attempted to maintain CLTX at an average level of 85±4 %$\dot{V}O_2$ peak for as long as possible. All Ps terminated CLTX due to shortness of breath; the mean number of minutes of CLTX was 9±1. At rest, the diaphragmatic time-tension index (TTdi) was .018±.003 and it reached a maximum of .049±.005 during CLTX. During the CLTX, gastric pressure (Pga) at the beginning of inspiration was usually greater than Pga at the end of inspiration; however, Pga remained positive with respect to the atmosphere throughout all tests. Additionally, electromyograms of the diaphragm (via esophageal electrodes), the inspiratory intercostals and the sternomastoid showed no consistent change in either the centroid frequency or the high-to-low ratio (i.e., the ratio of the power contained in the 125-250 Hz band to the power contained in the 25-50 Hz range) during CLTX. We conclude that VMF does not limit high-intensity CLTX in older male patients with COPD. Rather, dyspnea appears to terminate this type of exercise prior to the development of ventilatory muscle fatigue.

22.3

HYPERCAPNIA POTENTIATES VENTILATORY RESPONSIVENESS TO MODERATE EXERCISE IN HUMANS. C.S. Poon* and J.G. Greene* (SPON: S.A. Ward). North Dakota State Univ., Fargo, ND 58105 and Veterans Administration Hospital, Fargo, ND 58102.

Previous studies have yielded conflicting results on the ventilatory response to CO_2 during muscular exercise. To obviate possible experimental errors contributing to such variability we have examined the CO_2-exercise interaction in terms of the ventilatory response to exercise under conditions of controlled hypercapnia. Eight healthy adults underwent a sequence of 5-min incremental treadmill exercise from rest up to a maximum $\dot{V}CO_2$ of approximately 1.2 L/min in four successive steps. The arterial PCO_2 ($PaCO_2$) at rest was stabilized at the control level or up to 14 Torr above control by adding 0-7% CO_2 to the inspired air. Arterial isocapnia ($\Delta PaCO_2$=±1 Torr) was maintained from rest to exercise by continual adjustment of the inspired PCO_2 throughout the test. At all $PaCO_2$ levels the response in total ventilation ($\dot{V}_E$) was linearly related to exercise $\dot{V}CO_2$. Hypercapnia resulted in corresponding increases in both the slope (S) and zero-intercept (Vo) of the $\dot{V}_E$-$\dot{V}CO_2$ curve; the increases being proportional to the rise in $PaCO_2$ ($\Delta S/\Delta PaCO_2$=2.73±0.28 /Torr; $\Delta \dot{V}o/\Delta PaCO_2$=1.67± 0.18 L/min/Torr). Thus, the ventilatory response is characterized by an additive-plus-multiplicative interaction between the two stimuli. The result suggests that the traditional simple reflex model for ventilatory control may not completely account for the hyperpneas of exercise and CO_2 stimulation (Supported by NIH HL-30794, RR-07206, RR-02142, and AHA DA-G-19).

22.4

EFFECT OF HEAVY TREADMILL EXERCISE ON ARTERIAL pH (pHa) AND P_{CO_2} (Pa_{CO_2}) IN PONIES WITH AND WITHOUT CAROTID CHEMORECEPTORS. L.G. Pan*, H.V. Forster, G.E. Bisgard and C. Flynn*. Dept. Physiol., Med. Coll. Wis., Milwaukee, WI; V.A. Med. Ctr. Wood, WI; & Dept. Structure and Function, Vet. Sci., Univ. Wis., Madison, WI 53706

We have reported arterial hypocapnia and alkalosis during mild to moderate exercise in ponies (JAP 54:1394-1402, 1982). The present study addressed the pHa and Pa_{CO_2} responses in ponies during heavy treadmill exercise at 5-7 mph with a 15-20% grade. Eight ponies with intact carotid bodies and 5 ponies 2-4 years post carotid body denervation (CBD) were subjected to 6 min periods of exercise. Arterial blood was sampled continuously throughout rest and exercise. In 6 of 8 ponies with carotid bodies intact, pHa decreased from 7.392± .03 (SD) at rest to 7.261±.12 by 6 min of exercise. Pa_{CO_2} decreased from 41.8±2.0 mmHg to 30.7 ±1.8 mmHg with exercise over the same time interval. In two other normal ponies, pHa remained at resting levels (pHa=7.446 at 6 min) yet Pa_{CO_2} decreased from 44.8 to 31.3 mmHg by 6 min of work. In 5 CBD ponies, pHa decreased from 7.397±.02 at rest to 7.269±.10 with exercise (6 min) while Pa_{CO_2} decreased from 43.3±2.9 (SD) mmHg to 31.6±3.8 mmHg (6 min). Conclusions: 1) arterial acidosis is not requisite for the hyperventilation during heavy exercise in ponies; 2) pHa stimulation at the carotid body in ponies is not essential for the hyperventilation at this work intensity. (Support Med. Res. Serv. of VA, USPHS 25739)

22.5

TEMPORAL PATTERN OF Pa_{CO_2} DURING TREADMILL EXERCISE IN HUMANS H.V. Forster, L.G. Pan*, and A. Funahashi*. Dept. of Physiology Med. Col. Wis. and Wood VA Med. Ctr., Milwaukee WI 53193

A radial or brachial artery was catheterized in 9 adults. After sampling blood during supine and standing rest the subjects either walked for 5 min at 2 mph-0% grade followed by 3 min of running at 6 mph-0% or they ran for 5 min and then walked for 3 min. Blood was sampled at 15 sec intervals during the first min of work transitions and over 30 sec intervals thereafter. Resting Pa_{CO_2} during supine and standing postures was 40.7±0.5(SE) and 38.5±0.4 mmHg respectively (P<.001). Relative to supine and stand rest, 6 of 9 subjects were consistently hypocapnic (1-3 mmHg) during the first min of exercise and during the walk to run transition. When the data from all subjects were pooled, there was no significant hypocapnia inthe stand rest-work transitions or in the work to work transitions (P>.10). Steady-state Pa_{CO_2} was 38.9±0.6 and 38.3±0.6 at 2 and 6 mph respectively (P<.025). These values differed significantly from supine rest (P<.001). A mouthpiece breathing valve system was not used in these studies. However, while breathing through this system, the hypocapnia during rest to work transitions was accentuated 1.2 mmHg by increasing P_{IO_2} to 250 mmHg, (P<.05). Conclusions: 1) The posture related changes in Pa_{CO_2} at rest complicate interpretation of the exercise $PaCO_2$. 2) Nevertheless, it appears that the exercise response is not inherently isocapnic. 3) The carotid chemoreceptors normally minimize disruptions in Pa_{CO_2} during exercise. Support Med. Res.Serv. of VA and USPHS 25739.

22.6

DYNAMIC CHARACTERISTICS OF THE PERIPHERAL CHEMOREFLEX LOOP IN CATS. J. DeGoede,* A. Berkenbosch,* C.N. Olievier* and D.S. Ward* (SPON: S. Sullivan) Leiden University, Department of Physiology The Netherlands and UCLA Department of Anesthesiology, Los Angeles, California 90024.

Using the technique of the artificial brainstem perfusion (Berkenbosch et al., Respir. Physiol. 37:374, 1979), the kinetics of the peripheral ventilatory response following isoxic square waves and occasionally single on- and off steps in $PETCO_2$ (range 5 to 30 torr) was assessed in 12 anesthetized cats (chloralose-urethane) keeping the brainstem $PaCO_2$ and PaO_2 constant. In 27 of the 104 runs (66 during normoxia and 38 during hypoxia at a $PETO_2$ of about 65 torr) the ventilatory ontransient started with a clear "one sigh" peak ventilation. Ignoring this feature, 81 runs fitted reasonably well with the peripheral one compartment model as proposed by Bellville et al (J.A.P. 46:843, 1979), allowing for trend in the data. The remaining 23 runs contained a significant second component as analyzed with a two compartment model, with a time constant ranging from 28 to 3500 seconds. Of these 23 runs, 11 were from one cat out of a total of 13 runs. The mean time constant and time delay (with standard deviation) of the fast component during normoxia were 3.7 ± 1.6 s and 4.1 ± 0.8 s respectively. During hypoxia these values were 4.5 ± 2.4 s and 3.1 ± 0.8 s.

Our data suggest that the peripheral chemoreflex loop is adequately described with one fast component.

22.7

EFFECT OF DOPAMINE ON THE VENTILATORY RESPONSE TO CO_2 IN CATS A. Berkenbosch*, J. DeGoede*, C.N. Olievier* and D.S. Ward*. (SPON: S. Sullivan) Leiden University, Department of Physiology The Netherlands and UCLA Department of Anesthesiology, Los Angeles, California 90024.

In 9 anesthetized cats (chloralose-urethane) the ventilatory response to $PETCO_2$ steps at normoxia was studied before and after i.v. infusion of dopamine (7 $ug.kg^{-1}.min^{-1}$). The response was separated into a slow (central) and fast (peripheral) component using a two-compartment model (Bellville et al. JAP 46: 843, 1979). Upon dopamine infusion there were no significant changes in the CO_2 sensitivities and time constants of the central and peripheral components. However, the intercept of the steady-state CO_2 response curve at zero ventilation was significantly increased (mean 3 torr; P<0.01).

In 3 additional cats the CO_2 response of the peripheral chemoreflex loop was measured using the artificial medullary perfusion technique (Berkenbosch et al., Respir. Physiol. 37: 374, 1979). Systemic i.v. infusion of dopamine caused a parallel shift of the peripheral ventilatory response curve to the right. Administering dopamine (one tenth of the systemic dose) to the blood perfusing the medulla oblongata had no effect on ventilation.

We conclude that in normoxic cats the parallel shift of the ventilatory response curve to CO_2 as caused by dopamine is due to a tonic inhibitory effect on the peripheral chemoreflex loop.

22.8

VENTILATORY SENSITIVITY TO CO_2 DURING HYPOCAPNIA IN AWAKE SPONTANEOUSLY BREATHING DOGS. R.D. Tallman Jr., R. Marcolin,* M. Howie,* and J.S. McDonald.* Dept. of Anesthesiology, Ohio State Univ. Cols. Oh. 43210

Although the cardiopulmonary responses to elevated $PaCO_2$ have been extensively studied, reductions in CO_2 delivery below the normal value in awake, spontaneously breathing animals are not well understood. To study this problem we used an extracorporeal veno-venous circuit to unload CO_2 from the venous blood (UL) in 6 dogs (avg. wt. 31 kg). A chronic tracheostomy was performed 1 month prior to the study. Femoral vascular shunts were implanted 3 days before the study with the right venous catheter extending to the thoracic vena cava. Venous blood was drained from this catheter and pumped through two silicone membrane gas exchangers and returned through the opposite femoral vein. UL was accomplished by ventilating the membrane lungs with air; the level of UL was chosen just prior to reaching apnea. Either 2% CO_2 inhalation (IL) or UL were randomly assigned and bracketed by a control state. Inspired O_2 was adjusted to maintain end tidal O_2 at the control levels. All measurements were made in the steady state. The average CO_2 sensitivity during IL was 2.1 l/min/Torr. During UL, a hypocapnic hypopnea resulted with a sensitivity of 1.7 l/min/Torr. There is no statistical difference between these slopes. These results show that the CO_2 sensitivity curve in normoxia continues through the operating point without a change in slope. The apneic threshold is therefore a function of the CO_2 sensitivity and the resting level of ventilation. (Supported in part by NIH Grant HL 29715).

22.9

BIPHASIC ALTERATION OF THE VENTILATORY RESPONSE TO CO_2 IN NEWBORN RATS AFTER CHRONIC MATERNAL HYPERCAPNIA. K.L. McGilliard* (SPON: David C. Randall). Dept. of Pharmacology, Univ. of Kentucky, College of Medicine, Lexington, KY 40536.

Altered chemoreceptor development during the fetal period may lead to hypoventilation, apnea spells and sudden infant death syndrome. To test the effect of fetal exposure to hypercapnia on the development of central chemoreceptors, pregnant rats were exposed to 0%, 5% or 10% CO_2 in an environmental chamber throughout gestation. Ventilation was measured in the unanesthetized offspring at 1, 7, 14 and 21 days of age using a volume-displacement body plethysmograph. Total ventilation ($\dot{V}_E$) was slightly increased over control in both CO_2-exposed groups at all ages. CO_2-response was assessed using steady-state methods. Plots of % change in $\dot{V}_E$ or tidal volume (V_T) vs. % inspired CO_2 were linear over the range of 1-6% CO_2 at all ages. Only 21-day-old rats exhibited a positive respiratory rate (f) response to CO_2. Slopes of the $\dot{V}_E$-CO_2 response curves of 5% and 10% CO_2-exposed rats were significantly increased over control at 7 days, but not different from control at 14 days. The increase in slope was due to an elevated V_T response to CO_2. In contrast, slopes at 21 days were significantly decreased in both CO_2-exposed groups compared to control. The decrease in slope was due to a smaller f response to CO_2, with no change in V_T response. The biphasic alteration of CO_2-sensitivity suggests that two different mechanisms may be involved in the adaptation to chronic prenatal hypercapnia. Supported by PSP Fund of the Univ. of Kentucky.

22.10

EFFECT OF DOPAMINE ON HYPOXIC-HYPERCAPNIC INTERACTION. D.S. Ward* and S.J. Sabol* (SPON: S. Sullivan) Dept. of Anesthesiology Univ. of California, Los Angeles, CA 90024.

Dopamine is an endogenous catecholamine with neurohumoral activity in both the central and peripheral nervous systems, including the carotid body. It has recently been shown that low-dose intravenous dopamine can decrease hyperpnea due to hypoxia. Investigations have shown both a large (75%) decrease (Ward and Bellville JAP 55:1418, 1983) and a small (24%) decrease (Olson et al. ARRD 126:783, 1982) in hypoxic hyperpnea during dopamine infusion. The purpose of this study was to reconcile the apparent discrepency. Both with and without dopamine 3 mcg/kg/min infusing, four healthy male subjects were gradually rendered hypoxic at each of three CO_2 levels. At a constant end-tidal CO_2, a 1-minute hypoxic ramp which lowered end-tidal O_2 from approximately 14% to 7% was followed by two minutes of constant hypoxia. Three minutes after an abrupt return to normoxia the hypoxic ramp was repeated. The decrease in absolute hypoxic sensitivity was approximately the same at all CO_2 levels. As CO_2 increased, the change in hypoxic sensitivity with dopamine represented a declining % of absolute hypoxic sensitivity. This resulted in dopamine causing an average 75% decrease in hypoxic sensitivity during eucapnia ($p<.05$), and an average decrease of 35% at 6.4% CO_2 and 24% at 7% CO_2 ($p>.05$). Low-dose intravenous dopamine is a depressant of hypoxic hyperpnea at eucapnia, but does not affect the hypoxic-hypercapnic interaction.

22.11

EFFECTS OF TONIC VAGAL INPUT ON BREATHING PATTERN IN NEWBORN RABBITS. Teresa Trippenbach, Gisele Kelly* and Daniel Marlot*, Dept. Physiol., McGill Univ., Montreal, Quebec H3G 1Y6

Respiratory effects of positive and negative pressure breathing were studied in 1 day-old rabbit pups anesthetized with ketamine (50 mg/kg i.m.) and acepromazine (3 mg/kg, i.m.). We recorded tidal volume (V_T), tracheal pressure (P_{tr}) and, integrated diaphragmatic EMG (DiEMG). Inspiratory (T_I) and expiratory time (T_E) were measured from the records of DiEMG. When P_{tr} decreased 1 and 2 cmH_2O, minute ventilation ($\dot{V}_E$) increased due to an increase in respiratory rate (f). Increase in f relied on shortening of both T_I and T_E; T_E effect being more pronounced. DiEMG and its rate of rise ($DiEMG_t$) also increased. During breathing with increased P_{tr} by 1 or 2 cmH_2O, $\dot{V}_E$, f, and V_T decreased. Changes in f relied on a T_E prolongation. Neither DiEMG nor $DiEMG_t$ were affected. Except for V_T decrease during positive P_{tr}, all other effects disappeared after vagotomy. Our results indicate that an increase in tonic vagal activity interacts with the mechanisms controlling T_E. Since at FRC there is none or very little active stretch receptors in newborns, it is unlikely that further decrease in their activity is responsible for changes in the breathing pattern and DiEMG during lung deflation. Because of the nature of the stimulus and the long lasting effect we must exclude the pulmonary J and irritant receptors as the source of this response. We propose the atrial vagal receptors as a possible respiratory excitatory input that is triggered by increased venous return and distension of the left heart developed during lowered intrathoracic pressure.

Supported by the MRC of Canada.

22.12

CHARACTERISTICS OF "FLOW" RECEPTORS IN THE LARYNX. G. Sant'Ambrogio, O.P. Mathew and F.B. Sant'Ambrogio. Department of Physiology and Biophysics and Department of Pediatrics, University of Texas Medical Branch, Galveston, Texas 77550.

We have documented the presence of cold sensing endings in the larynx that function as inspiratory flow detectors and have fibers running in the superior laryngeal nerve (Fed. Proc. 43:814, 1984). These receptors are activated by airflow through the isolated "in vivo" upper airway, either in an inspiratory or expiratory direction, provided that the airflow lowers the laryngeal temperature below 36°C. These endings have a high dynamic sensitivity as measured by their adaptation to constant airflow. We have localized 8 of these endings on the exposed luminal surface of the larynx. Mechanical probing "per se" did not stimulate these receptors unless the probe was kept below tissue temperature. Cold air jets were also effective in stimulating these endings and could, similarly, pinpoint the receptor field. All 8 receptors were located on the vocal cords (one contralaterally): one on the edge, three on the cranial and four on the caudal surface. Topical anesthesia with 2% lidocaine blocks these receptors in 2-3 seconds indicating a very superficial location. Because of their superficial location and their high dynamic sensitivity these endings are well suited to detect changes in inspiratory airflow.
(Supported by NIH grants HL-20122 and HL-01156).

CARDIAC AND SKELETAL MUSCLE

23.1

Effects of Stimulus Frequency, Resting Length, pHe and Caffeine Upon Na and Ca Transport in Rat Papillary Muscles. Robert B. Tallitsch, Augustana College, Rock Island, IL. 61201

Earlier resports indicated that papillary muscles isolated from the posterior RV of 6 mo. virgin male Wistar rats exhibit a constant rate coefficient for both Na and Ca transport after the first 20 min. of efflux experiments. Work with ouabain, O Na e and O Ca e indicate the presence of a ouabain sensitive and an ouabain-insensitive component to the Na efflux. The ouabain-insensitive component is composed of, at least in part, of a Na-Ca countertransport system. Further work with stimulus frequency, resting length, pHe and caffeine show an alteration of Na-Ca countertransport. Variations in stimulus frequency from 0.4/sec to 0.8/sec to 1.2/sec caused the expected negative staircase and an increased Na transport and decreased Ca transport activity. Varying resting length from 50% Lmax to 80% Lmax to Lmax caused the expected increase in developed tension and an increased Na transport and a decreased Ca transport activity. Variations in pHe did not alter Na trasnport activity, but did alter Ca transport kinetics. 2 mM caffeine decreased developed tension 75.5 $\pm$ 5.3%, increased Ca efflux 210.3 $\pm$ 15.7% and decreased Na efflux 87.3 $\pm$ 9.1%. A dose-response relationship was obtained for all variables. Taken together these results continue to characterize Na and Ca transport in this preparation, and continue to indicate its viability for such studies.

23.2

CALCIUM-SODIUM RATIOS AS DETERMINANTS OF FUNCTION OF THE ISOLATED, ISOMETRIC KITTEN PAPILLARY MUSCLE. Fereydoon Sadri* and Norman F. Paradise. Dept. of Physiology, Northeastern Ohio Universities College of Medicine, Rootstown, Ohio 44272.

It has been suggested that the stoichiometry of calcium - sodium exchange across the cardiac sarcolemma is one calcium ion for two sodium ions or one calcium ion for three sodium ions. Our experiments were undertaken to test both hypotheses. The papillary muscle from the right ventricle of the kitten heart was arranged to contract isometrically and submerged in continuously oxygenated (95% O_2 - 5% CO_2) physiologic salt solution (T=30 °C; pH=7.4). Tension twitches were recorded at 8 stimulation rates ranging from 30 beats per min to one beat per 6 min. There was a significant increase in tension development at the higher and intermediate contraction frequencies (range: 30 beats per min to 2 beats per min) when $(Na^+)_o$ was reduced from 140 mM to 105 mM or 70 mM (and replaced by choline) even though $(Ca^{++})_o/(Na^+)_o^2$ was constant. Time-to-peak tension was significantly reduced over almost the entire range of contraction frequencies when $(Na^+)_o$ was 70 mM. Similar changes in tension and time-to-peak tension were observed when $(Na^+)_o$ was reduced to 105 mM or 70 mM but with $(Ca^{++})_o/(Na^+)_o^3$ constant. These data demonstrate that maintaining the constancy of either $(Ca^{++})_o/(Na^+)_o^2$ or of $(Ca^{++})_o/(Na^+)_o^3$ does not assure that muscle function will remain unchanged when decreases in $(Ca^{++})_o$ and $(Na^+)_o$ are produced. This may indicate that one calcium ion exchanges for more than three sodium ions. (Supported in part by the Akron District Chapter of the AHA).

23.3

THE INOTROPIC ACTION OF STROPHANTHIDIN AT DIFFERENT SODIUM AND CALCIUM CONCENTRATIONS. M. Vassalle, R. Bernabei*, Pier U. Carbonin* and Tung Li*. SUNY, Downstate Med. Ctr. Brooklyn, N.Y. 11203.

The role of sodium (Na) and calcium (Ca) in the inotropic effect of low and high strophanthidin concentrations was investigated in canine cardiac Purkinje fibers perfused in vitro. The following results were obtained. High ($1-5x10^{-7}$M) strophanthidin: 1) increases percentagewise the contractile force more in low Ca than in any other solution tested; 2) increases force least when both Na and Ca concentrations are less than normal; 3) increases force more in high Na than in Tyrode solution; 4) re-increases force when the force has been decreased by low Ca; 5) induces a transient increase in force when Na is lowered after a low calcium exposure or a low Na-Ca exposure; 6) induces contracture when Na (but not Ca) is restored to normal in the presence of metabolic inhibitors. A low ($3-5x10^{-8}$M) strophanthidin: 7) potentiates and is potentiated by norepinephrine ($5x10^{-8}$M) and high calcium (4 mM); 8) re-increases the force little in the presence of low Ca; 9) allows low Na to increase force more than in Tyrode solution; 10) is depressed in its inotropic effect by Mn as much as in Tyrode solution. It is concluded that the inotropic effect of large concentrations of strophanthidin is markedly influenced by sodium but that the inotropy of small concentrations of strophanthidin can be dissociated from an exclusive role of that ion.

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23.4

INTERACTIONS OF SEX STEROIDS UPON MYOCARDIAL INOTROPIC AND CHRONOTROPIC RESPONSES TO NOREPINEPHRINE. G.M. Brenner,* L.G. Martin, L.C. Wince,* M.W. Banschbach,* and K.L. Jarolim*. Oklahoma Coll. Osteopathic Med., Tulsa, OK 74107

Chronic estrogen treatment has been shown to reduce cardiac beta adrenergic responsiveness. The present studies examined the interaction of chronic estradiol (E) and testosterone (T) treatments on myocardial inotropic and chronotropic responses. Groups of ten CD strain castrate male or female rats were injected daily for 16 weeks with 0.1ml of cottonseed oil or with oil containing estradiol benzoate (7 ug/100g), testosterone propionate (50 ug/100g), or a combination of both hormones. After completing treatments, the response of isolated atria to the positive chronotropic (PC) and inotropic (PI) effects of norepinephrine (NE) was determined. In females, E significantly reduced the maximum PC effect of NE to 77% of controls (C). T produced a smaller reduction of the maximum PC effect of NE (86% of C), whereas the maximum PC effect in animals receiving E and T was 93% of C. In contrast to these results, E significantly increased the PC response to NE in males (121% of C). The effects of T or both E and T were not significantly different from C. These studies indicate that the effect of E on beta adrenergic responsiveness is dependent on the genetic sex of castrate animals and affects inotropic and chronotropic responses differently. T appeared to antagonize the effect of E when both steroids were administered.

23.5

Myoglobin (MGB) Facilitates O_2 Diffusion in Mammalian Myocardium (Kitten Papillary Muscle). E.A. Braunlin, G.M. Wahler, R.V. Lucas, Jr.*and I.J. Fox. University of Minnesota, Minneapolis, MN 55455.

To test for a functional role for MGB, developed tension and $\pm dT/dt$ were studied for 90 min in 7 groups of isolated, kitten papillary muscles (dia: <0.7 mm) stimulated at 24/min, 30°C, pO_2 450 mmHg:I, controls (N=7);II, after glycolytic blockade with 10^{-4}M iodoacetate (N=6); III, after glycolytic blockade followed by MGB inactivation by $2x10^{-3}$M $NaNO_2$ (N=6); IV, after glycolytic blockade followed by MGB inactivation at a pO_2 of ≈600 mmHg (N=4). Ten min after adding $NaNO_2$, the relaxation rate ($-dT/dt_{max}$) of group III muscles decreased compared to that of group II with glycolytic blockade alone ($P<0.05$), a decrease prevented in group IV by raising the pO_2, indicating it was due to a specific effect on MGB by $NaNO_2$. The effects of iodoacetate (II, N=6) in decreasing $+dT/dt_{max}$ and of $NaNO_2$ (V, N=3) in decreasing $-dT/dt_{max}$ were also specific since the former was prevented by adding pyruvate $2x10^{-3}$M (VI, N=3) and the latter by raising bath pO_2 to≈600 mmHg (VII, N=3). We conclude that in mammalian myocardium:1) facilitation of O_2 diffusion by MGB helps maintain mechanical function e.g. maximal rate of relaxation and 2) the maximal rate of relaxation is a sensitive indicator of myocardial oxygenation.

23.6

MYOFIBRILLAR CREATINE KINASE COMPONENT OF PHOSPHORYLCREATINE SHUTTLE IS NOT INFLUENCED BY HYPOTHYROIDISM. R.T. Dowell. Department of Physiology. University of Kansas Medical Center. Kansas City, KS 66103.

Myofibrillar energy utilization via ATPase is supported by localized creatine kinase (CK) in the phosphorylcreatine shuttle proposed by Bessman et al. (Science 211:448, 1981). Because cardiac myofibril ATPase is transcriptionally regulated by thyroid hormone, the present studies examined whether parallel CK regulation occurs. Adult rats were made hypothyroid by daily injection (10 mg/kg,ip) of propylthiouracil (PTU). Controls received drug vehicle. After 4 wks, rats were exsanguinated and the heart removed. LV tissue was dissected. Purified myofibrils were analyzed for ATPase and CK activities. PTU treatment reduced plasma levels of T4 (ug/dl) and T3 (ng/dl). As expected, both magnesium-activated ATPase and calcium-activated ATPase were significantly reduced in PTU myofibrils. CK activity was not significantly altered in myofibrils from PTU-treated rats.

	T4	T3	Mg-ATPase	Ca-ATPase	CK
Control(5)	4.82±.49	88±12	143±15	392±48	435±72
PTU(5)	1.16±.07*	13±3*	102±9*	90±7*	389±76

Values are mean ± SE. *$P<0.05$ vs control. No. of animals in parentheses. Enzyme activities are nmole/mg/min.

Results suggest that cardiac myofibrillar ATPase and CK are not regulated by comparable mechanisms. (Supported by HL28456 and HD16247).

23.7

MYOCARDIAL ADAPTATIONS OF CHRONICALLY PACED NORMAL PIG HEARTS. C.D. Ianuzzo, S. Brotherton*, J. Easdown* and T. Salerno*. York University, Toronto, Ont. M3L 1P3 and University of Toronto, Toronto, Ont. M5B 1W8.

We hypothesized that chronically imposed tachycardia would induce increases in enzymatic potential for energy transduction and alter the phenotypic expression of the ventricular myosin isozyme from V_3 towards V_1. Cardiac pacemakers were surgically implanted in Yorkshire pigs with initial body weights of 20-25 kg. The hearts were paced at 180 beats per min, which was approximately twice the resting rate, using Medtronic unipolar pulse generators. Sham operated animals had an epicardial lead surgically implanted in the left atrium. After a minimal of 35 days of cardiac pacing, animals were anesthetized with pentobarbitol and pentothal. Following selected hemodynamic measurements, portions of the ventricles were excised for biochemical analyses. The maximal enzyme activities of phosphofructokinase, citrate synthase and β-hydroxyacyl-CoA dehydrogenase were higher in the paced than in the non-paced hearts. Electrophoretograms of the native pyrophosphate gels indicated that the myosin phenotype was not altered by cardiac pacing. We concluded that chronic tachycardia via cardiac pacing increases the capacity for energy transduction but does not alter myosin isozyme expression in the swine myocardium.

Supported by Ontario Heart Foundation and Canadian NSERC grants.

23.8

^{31}P-NMR STUDIES OF METABOLITE LEVELS IN SINGLE BARNACLE MUSCLE FIBERS. John Hansen*, Timothy Sharpe*, E. Edward Bittar. School of Pharmacy and Department of Physiology, University of Wisconsin, Madison, WI 53706.

Meaningful ^{31}P-NMR spectra can be collected from a single barnacle muscle fiber at rest some 30 mins after dissection from the muscle. Typical spectra show weak resonances for sugar phosphates and P_i, and prominent resonances corresponding to the phosphate group of ArP and the three phosphates of ATP. By using 1M methylene diphosphonic acid as a standard, it is possible to quantitate the resonances. The results obtained with 8 fibers suspended in artificial seawater prepared in D_2O are as follows (mmoles/kg fiber water; 25°C): SP = 2.7 ± 0.3 (SEM); P_i = 2.69 ± 0.52; ArP = 24.18 ± 1.8; and β-ATP = 4.7 ± 0.47. The ArP value is slightly higher than that obtained using enzymic fluorimetry. The value for β-ATP agrees with that found by means of firefly and isotachophoresis. Experiments examining ^{31}P-spectra as a function of time show a steady rise in SP and P_i and a running down of ArP stores. Plots of the ArP/ArP + P_i ratio vs time give a single straight line. These results are in keeping with the view that ArP in resting fibers is the immediate buffer of ATP.

23.9

CALCIUM CAPACITY AND UPTAKE RATE IN SKINNED FIBERS OF MYODYSTROPHIC MUSCLE. Bert A. Mobley. University of Oklahoma, Oklahoma City, OK 73190.

Parameters related to the capacity and the rate of uptake of calcium ions by sarcoplasmic reticulum (SR) were measured in skinned extensor digitorum longus fibers of control and myodystrophic mice. Skinned fibers were mounted on a force transducer and apparatus for changing the bathing solution. T = 25° C. To test the capacity of the SR, fibers were placed in a solution for maximal loading and then moved to a solution in which the major anion, gluconate, in the relaxing solution was replaced by chloride. In the resulting contractures, the means of the forces produced by 10 control and 10 myodystrophic fibers were not significantly different. The conclusion is that the capacities of SR for calcium in the two types of fibers are equivalent. To test the rate of loading of SR, 11 control and 11 myodystrophic fibers were depleted of calcium. Then they were placed in a solution with pCa = 5.5, and the delay before a contracture began was recorded. The delay was the time required for the SR to load and reach a threshold for calcium-induced-calcium-release. The mean delay in control fibers was significantly less than in myodystrophic fibers. The disparity in loading times probably reflected a difference in the activities of the calcium pumps or a difference in the number of pump sites. Valinomycin (5 μM) did not significantly alter the loading times of either type of fiber. (Supported by USPHS RO1 NS 16989.)

23.10

DISTRIBUTION OF Ca^{2+}-PULSE INDUCED Ca^{2+} EFFLUX CHANNEL IN SKELETAL SARCOPLASMIC RETICULUM FRACTIONS. T.E. Nelson, The University of Texas Medical Branch, Galveston, TX 77550.

Specific experimental conditions can demonstrate Ca^{2+}-induced Ca^{2+} release ($Ca^{2+} \sim Ca^{2+}R$) from fragmented sarcoplasmic reticulum (SR) isolates. The putative Ca^{2+} channel for $Ca^{2+} \sim Ca^{2+}R$ is postulated to reside in the SR terminal cisternae. To test this theory, the activities for inward Ca^{2+} transport (Ca^{2+} pump) and for $Ca^{2+} \sim Ca^{2+}R$ channels were measured in 4 different SR fractions (1=8-10,000; 2=10=12,000; 3=12-20,000; and 4=20-48,000 x g). Rate of ATP-driven Ca^{2+} transport and percent of Ca^{2+} pump protein were greater in less dense SR fractions. (1=11.8; 2=15.3; 3=16.6; 4=26.4 nmoles/sec x mg). In contrast, amount of $Ca^{2+} \sim Ca^{2+}R$ channel activity was higher in SR fractions of greater density. Optimal assessment of $Ca^{2+} \sim Ca^{2+}R$ channels, using quercetin, found release rates as follows: 1=44.6; 2=45.1; 3=26.6; 4=21.7 nmoles Ca^{2+}/sec x mg. The threshold Ca^{2+} preload for $Ca^{2+} \sim Ca^{2+}R$ did not differ significantly among the 4 SR fractions (1=136; 2=127; 3=135; 4=132 nmoles Ca^{2+}/mg), suggesting a common Ca^{2+} channel that has a higher distribution among heavier SR membranes. Results of this study support the thesis that Ca^{2+} release channels are more prevelant in heavy SR fractions (i.e. terminal cisternae and/or T-tubules) while the Ca^{2+} pump is in greater proportion in the longitudinal elements of the SR.

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23.11

CORRELATION OF *in vitro* HALOTHANE TEST WITH GENETIC SUSCEPTIBILITY IN MALIGNANT HYPERTHERMIA PIGS. Wilfried Ilias*, Charles H. Williams, Robert T. Fulfer*, Susan E. Dozier*, John Joyner* and Phool Chandra* Departments of Anesthesiology and Biochemistry, Texas Tech Regional Academic Health Center, El Paso, TX 79905.

MH susceptible pigs were challenged with 4% halothane for 3 min. and 2% halothane for up to 20 min. at the farm. Surgical cutdowns were completed under pentothal (22 mg/Kg) for invasive monitoring of AP, CVP, PAP, PAP_w, cardiac output, core and rectal temperature, end tidal CO_2, arterial and venous O_2 saturation and heart rate. *Gluteus maximus* muscle specimens (13) were tested *in vitro* in modified Krebs-Ringer solution (37°C) areated with 5% CO_2 in O_2, stimulated directly (1 msec, 0.2 Hz) under supramaximal conditions. Muscle strips were exposed to halothane (4%, 10 min.) after they had reached a steady state. MH x MH pigs (4) showed an increase in heart rate during invasive monitoring and 8 to 28% increase in baseline (contracture) *in vitro*. MH x N pigs (7) all showed increased heart rate during invasive monitoring and a 0 to 100% increase in baseline (contracture) *in vitro*. N x N pigs (2) showed no change in baseline when exposed to halothane *in vitro*. Changes in twitch response were not correlated with MH susceptibility. The halothane test at the farm misses 25-35% of the MH susceptible pigs. A more quantitative test for baseline change (contracture) is needed.

23.12

THE EFFECT OF PROPRANOLOL INFUSION AND HYPERCAPNIA ON SKELETAL MUSCLE METABOLISM B. Wolfe*, J.K. Barclay, T.E. Graham, J. Van Dijk* and B.A. Wilson*. Univ. of Guelph, Guelph, Canada.

Denervated right and left canine gastrocnemius in situ (N=17) were used to identify the effect of B receptor activity on skeletal muscle metabolism. Twenty min of arterial infusion with .12 mg/min of propranolol (PROP) inhibited the response to 1 mM isoproterenol in dogs breathing either air (N=6) or 4% CO2 in air (N=6). Control dogs breathed air (N=5). The right muscle served as an unstimulated control. After the left muscle was stimulated for 10 min at 3Hz, both muscles were frozen in liquid N2. $\dot{V}O2$ and $\dot{Q}$ were not affected by PROP at rest or during contractions. Developed tension was unchanged. Decreases in glycolytic intermediates and in F6P/F1,6P, αGP/DHAP, and La/Pyr ratios were observed in resting PROP muscle. Contracting PROP muscles had decreased La release, DHAP and F6P/F1,6P ratio. Twitch to rest ratios for F6P, αGP, NAD+ and the αGP/DHAP ratio increased with PROP. Hypercapnia-PROP decreased arterial, venous and muscle La and muscle Pyr in resting and stimulated muscle from the air-PROP values. Although PROP lowered the glycolytic profile in both treatments, decreased La metabolism with acidosis persisted.

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SMOOTH MUSCLE

24.1

THE EFFECT OF STRAIN ON VASCULAR MUSCLE CELLS IN CULTURE, C.L. Seidel, C.L. Ives*, B. Vu*, S.L. Eskin*, Depts. of Med. and Surg., Baylor Col. Med., Houston, Tx., 77030.

In vivo experiments suggest that increased strain is a stimulus for vessel wall hypertrophy. The purpose of this work was to directly test this hypothesis by determining the effect of cyclical strain on the protein production and morphology of cultured vascular smooth muscle cells. Muscle cells, obtained from dog saphenous veins by enzyme dispersion, were grown for 3 days on a polyurethane membrane and then subjected to a 10% strain at 1 Hz for an additional 3 days. Since these conditions approximate the physiological strain that occurs in arteries in response to pulse pressure they represent an elevated strain for these venous smooth muscle cells. The cells were removed from the membrane by trypsinization, counted, and the total protein (Lowry), actin and myosin (SDS-PAGE) contents determined and compared to control cell cultures not subjected to strain. Strained cells demonstrated an increase (31%, $p<0.05$) in the amount of total protein per cell, but no change in actin or myosin per cell. Cellular orientation was no longer random but ordered, with the long axis of the cell perpendicular to the direction of strain. This change in orientation occured within 24 hrs. suggesting that it was the result of cell movement rather than the positioning of daughter cells. These results indicate that strain is a stimulus not only for increased protein production but also for the orientation of the muscle cell.

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24.2

DIFFERENCES BETWEEN VASCULAR AND CARDIAC MYOSIN HEAVY CHAIN WEIGHT, L.A. Schildmeyer*, C.L. Seidel (SPON. J.C. Allen) Depts of Med & Physiol, Baylor Coll Med, Houston, TX 77030

Smooth muscle has a slower shortening velocity than cardiac muscle which may be due to differences in the structure of the myosin molecule. This work was performed to determine if structural differences existed. Crude extracts of myosin, prepared from canine femoral artery (FA) and left ventricle (LV) using an extraction solution containing 100mM $Na_4P_2O_7$, 5mM EDTA, 2% BME, and 0.01% protease inhibitors, were first electrophoresed on a 3% polyacrylamide nondenaturing pyrophosphate (NPP_i) gel. Native myosins were identified on the gel by their high ionic strength CaATPase activities. The FA myosin band had a greater mobility than the LV myosin band which could be due to differences in charge or molecular weight (MW). To determine if this greater mobility was due to lighter myosin heavy chains (MHC), myosin bands from NPP_i gels were electrophoresed on a 1% SDS-5% polyacrylamide gel. The NPP_i FA myosin band separated into more than 1 band, each with a lesser mobility than the single band produced by the NPP_i LV myosin band, indicating that the MHCs of FA were of a higher MW. Therefore, the greater mobility of the FA myosin band on the NPP_i gel is not due to heavy chains of lower MW. Multiple VSM myosin bands on SDS polyacrylamide gels has been reported previously. These data indicate that there are structural differences between FA and LV myosins which include differences in MW and charge of the native molecule, as well as in the weights of the MHCs.

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24.3

INFLUENCE OF pH ON ISOMETRIC FORCE (P_0) DEVELOPMENT AND RELAXATION IN SKINNED VASCULAR SMOOTH MUSCLE. J. Gardner* and F.P.J. Diecke, Department of Physiology, UMDNJ-New Jersey Medical School, Newark, NJ 07103

Effects of pH on preparations of Triton X-100 skinned rat caudal artery (Stout and Diecke, J. Pharm. Exp. Ther., 225:102) were examined. Helically cut strips skinned and studied at pH 6.5 exhibited fast half times for contraction ($T_{0.5C}$=0.26±0.09 min) but slow relaxation half times ($T_{0.5R}$=11.14±2.88 min). At pH 6.7, 6.9 and 7.1 strips showed increasingly slower $T_{0.5C}$ and reduced $T_{0.5R}$. At pH 7.1, $T_{0.5C}$=1.13±0.44 min and $T_{0.5R}$=1.60±0.18 min. Analysis of successive contractions at each pH indicated slower $T_{0.5C}$ but similar $T_{0.5R}$. "Bracketed" contractions at pH 6.5 compared to those at 6.9 indicated low pH decreased P_0 (87±7%) and $T_{0.5C}$ (80±11%) but increased $T_{0.5R}$ by 4.5±2.2 fold (n=6). At pH 7.1, test relaxations showed no effect of "Ca^{2+} drop" solutions enhancing $T_{0.5R}$ (1.00±0.11, n=4), although addition of 6mM KH_2PO_4 increased $T_{0.5R}$ 2.7-fold (0.37±0.02, n=4). pCa-tension curves at the 4 pH values indicated no shift in half maximal activation (K_{50}) between pH 6.5 and 6.7, but a significant (P<0.001) shift in K_{50} between pH 6.7 ($[Ca^{2+}]$ = $4.5x10^{-7}$M) and pH 7.1 ($[Ca^{2+}]$ = $8.7x10^{-7}$M). We suggest pH changes can alter the contractile and relaxation responses in vascular smooth muscle and may have significant effects in both normal and pathophysiological conditions.

24.4

EFFECTS OF OUABAIN AND K^+-FREE SOLUTIONS ON ISOMETRIC FORCE AND AEROBIC GLYCOLYSIS IN AORTAS FROM ALDOSTERONE-SALT HYPERTENSIVE RATS. **Ellen G. McMahon and Richard J. Paul, Dept. of Physiology & Biophysics, Univ. of Cincinnati, Cincinnati, OH 45267-0576**

Aldosterone infused at 0.25 µg/hr for four weeks into uninephrectomized rats on 1% NaCl significantly elevated systolic blood pressure (194 ± 4 vs 119 ± 3 mmHg; P< 0.001). Isometric force (P_0) in response to 50 mM KCl was similar, 30.15 ± 1.71 mN/mm^2 and 24.28 ± 2.49 mN/mm^2 in aortas from normotensive control (C) and hypertensive rats (AHR), respectively. P_0 in ouabain (1 mM) and K^+-free solution were normalized to the KCl responses. For controls, P_0 increased monotonically in ouabain ($t_{½}$ = 30.5 ± 6.5 min); in AHR, P_0 was biphasic, with a rapid initial rise ($t_{½}$ = 4.8 ± 1.3 min; p < 0.005) followed by a steady decline. After 60 min, responses in AHR were significantly lower than C (21.9 ± 4.1 vs 46.5 ± 8.9%; p < 0.05). In contrast, the time course of P_0 in K^+-free solutions was similar (AHR: $t_{½}$ = 48.6 ± 6.5 vs C: 49.5 ± 7.2 min); P_0 after 60 min was depressed in AHR though not statistically different (AHR: 18.5 ± 7.8 vs C: 35.5 ± 6.2%). Aortic lactate production (J_{lac}) was stimulated in ouabain and K^+-free solution. After 30 min in ouabain, J_{lac} was increased by 110 ± 20% in C and 102 ± 26% in AHR and in K^+-free solution, 24 ± 4 and 38 ± 11%. This stimulated rate was maintained for at least an additional 60 min. These results indicate that vascular responsiveness to Na^+-pump inhibition is depressed in aortas from AHR and that aerobic glycolysis in rat aorta may not be specifically coupled to Na^+-K^+ pumping as reported in vascular smooth muscle from other species. (Supported by NIH 23240, HL06769 and AHA).

24.5

OUABAIN-INSENSITIVE, CHLORIDE-SENSITIVE Tl^+ UPTAKE BY CANINE ILIAC ARTERIES. P.K. Rangachari* and Deborah McWade* (Spon: E. Cosmos) Department of Medicine, McMaster University, Hamilton, Ontario, Canada, L8N 3Z5.

Tl^+ uptake by canine iliac arteries can be partitioned into an ouabain-sensitive and an ouabain-insensitive component. The former reflects uptake by the Na^+ pump (Rangachari, Hypertension, 5:436, 1983). The ouabain-insensitive component accounts for 37% of total uptake in Na^+ loaded arteries. Total replacement of external chloride reduced markedly (by 55%), the ouabain-insensitive component. Increasing external chloride under such conditions stimulated uptake with an apparent Km of 40mM. The chloride-sensitive component was inhibited by external Rb, the diuretic, MK196 and pCMBS. Neither the presence of ouabain nor the removal of chloride altered significantly the water contents of incubated tissues (as estimated from dry/wet weight ratios). It is thus unlikely that either of these components plays a significant role in the steady-state regulation of cell volume in this tissue.

Supported by the Canadian and Ontario Heart Foundations.

24.6

DEPENDENCE OF RESTING MEMBRANE POTENTIAL ON VESSEL DIAMETER IN CEREBROVASCULAR SMOOTH MUSCLE. T. Bun*, J.W. Peterson, S. F. Ronner*, J.F. Tomera*, and N.T. Zervas*. Neurosurgical Service, Massachusetts General Hospital, Boston, MA. 02114

1.5 cm segments of excised dog basilar artery were cannulated at each end and perfused with Krebs-Henseleit:5 mM glucose saline gassed with 20% O_2/5% CO_2 at 37°. Perfusion pressure was varied between 0 and 300 mm Hg at a constant flow of 0.5 ml/min. The vessel segment was simultaneously superfused with identical saline. Vessel diameter was measured directly from a video monitor. Vessel diameter increased approximately exponentially with increased perfusion pressure, reaching 80% of maximum dilation at 60 mm Hg. Microelectrode penetrations of 548 cells in 32 arteries were carried out and membrane potential recorded. Resting membrane potential (E_m) at 0 mm Hg averaged -53 ±1.0 mV (SEM, n=81). As distending pressure was increased in 15 mm Hg increments to 60 mm Hg, E_m progressively depolarized to -42 ±1.1 mV (SEM, n=34). Further increases in pressure gave only a small trend towards further depolarization, reaching -36 mV at 300 mm Hg. High-K^+ saline (78 mM) and Ca^{++}-free normal saline both depolarized E_m to -20 to -15 mV, while Mg^{++}-free normal saline depolarized E_m by only 5- 8 mV at all pressures. 10^{-5} M serotonin depolarized the vessel by 5-15 mV at all pressures and caused the pressure-dependent depolarization to occur at smaller vessel diameter. These observations are consistent with a membrane-based mechanism for pressure-dependent autoregulation in the cerebral vasculature. Supported by NIH Grants HL22573 and HL26023.

24.7

SMOOTH MUSCLE PLASMA MEMBRANE VESICLE ION PERMEABILITY; A NEW METHOD. A.K. Grover, A.P. Singh*, P.K. Rangachari*, and P. Nicholls*. Depts. of Neurosciences and Medicine, McMaster University, Hamilton, Ontario, Canada and Dept. of Biol. Sci., Brock University, St. Catharines, Ontario, Canada.

Rat myometrium plasma membranes (PM) were loaded with 8-hydroxytrisulfonopyrene (HSP) by including the dye in the homogenization media. The isolated PM vesicles contained trapped HSP. The trapped dye had a pH-dependent fluorescence with pK of 7.6. When the membranes were suspended in media containing tetramethylammonium (TMA)-glutamate (GLU), increasing the pH resulted in an instantaneous increase in fluorescence followed by a slow increase. The latter increase had a mean $t_{0.5}$ of 75.4 sec. FCCP or valinomycin (VAL) or FCCP + VAL did not influence this $t_{0.5}$. Addition of FCCP to the PM suspension in K-GLU also did not influence the slow release but an addition of VAL alone reduced the $t_{0.5}$ to about 50% and the addition of FCCP + VAL caused a very fast decay of the H^+-gradient. Thus the dissipation of H^+-gradient is limited by creation of a membrane potential the removal of which by movement of other ions is necessary. Using this principle the relative permeability of the PM vesicles to various anions and cations was monitored. The relative permeabilities of the cations were: TMA = K^+ < Na^+, and of the anions were: L-glutamate = D-glutamate < Cl < SO_4 < glutarate. Thus for the first time we have directly measured relative permeability of any smooth muscle PM vesicles to the various ions. This work was supported by grants from M.R.C. and N.S.E.R.C.

24.8

MECHANISM OF HYDRALAZINE-INDUCED RELAXATION OF ARTERIAL SMOOTH MUSCLE. **A.B. Ebeigbe, Dept. of Physiology, Med. Sch., University of Benin, Benin City, Nigeria.**

There are conflicting reports about the mechanism of hydralazine-induced relaxation of vascular smooth muscles (Mclean et al, 1978: J. Pharmacol. Exp. Ther. 207, 40-48; Lipe & Moulds, 1981: J. Pharmacol. Exp. Ther. 217, 204-208). The present study was designed to characterize hydralazine-induced relaxation in the rat tail artery. Isometric contractions were measured in helical strips of rat tail arteries bathed in Krebs solution at 37°C, pH 7.4. Hydralazine caused dose-dependent relaxation of contractile responses by 10^{-7}M norepinephrine(NE), 10^{-7}M 5-HT, or 100mM KCl (ID$_{50}$: $2.7(±0.6)x10^{-6}$; $3.2(±0.4)x10^{-5}$ and $1.8(±1.0)x10^{-5}$M respectively). $CaCl_2$ dose-response in the presence of 10^{-5}M NE, 10^{-5}M 5-HT or 100mM KCl was significantly inhibited by $5x10^{-4}$M hydralazine. The degree of inhibition of $CaCl_2$ dose-response curve was in the order:KCl 5-HT NE. Hydralazine ($5x10^{-4}$M) also inhibited $BaCl_2$ dose-response curve (in K^+-depolarized strips); the % reduction of maximal response to $BaCl_2$ was 87.4±1.5. In other experiments, hydralazine ($5x10^{-4}$M) significantly depressed (by 20%) the phasic contractile response to NE due to mobilization of Ca from a membrane-bound pool. These results suggest that in the rat tail artery, hydralazine interferes with Ca^{++} influx, as well as release from a membrane-bound pool.

***Supported by Uniben grant 60/227**

24.9

IN VITRO SPONTANEOUS MOTILITY RESPONSES OF RAT VAS DEFERENS AND SEMINAL VESICLES TO NOREPINEPHRINE,PHENYLEPHRINE, ISOPROTERENOL,HISTAMINE,TOLAZOLINE,TIMOLOL MALEATE, PROPRANOLOL AND OXYTOCIN. William P. Ventura. Pace University Pleasantville, N.Y. 10570.

Sixty rat vas deferens and seminal vesicles were used to study the effects of drugs on spontaneously active (non-electrically stimulated) tissues. Tissues removed intact(non-stripped;mounted in separate 25-ml organ baths;temp.39°C; pH 7.4; modified Locke's-glucose perfusion fluid; gassed with 95%O_2-5%CO_2. Spontaneous motility patterns were quantitatively reliable and repeatable for all tissues studied. All drugs tested in multiple microgram dose ranges and following types of receptors proposed for tissue responses to agents tested based on force (first arrow) and frequency (second arrow) responses: alpha 1↑↑;alpha 2↑↓;beta 2↓↑ ; beta 3 ↓↓ . Data suggest the following: Norepinephrine (alpha 1 agonist; beta 2 agonist after isoproterenol or tolazoline); Phenylephrine (alpha 1 agonist only); Isoproterenol (alpha 2 agonist; beta 2 agonist after tolazoline; alpha 1 agonistafter timolol maleate or propranolol); Histamine (alpha 2 agonist; beta 2 agonist after tolazoline;beta 3 after tolazoline plus timolol maleate);Timolol maleate and Propranolol (beta 2 agonist and antagonist; beta 3 agonist); Oxytocin (beta 2 agonist and antagonist for timolol maleate and propranolol). Timolol maleate and propranolol were the only agents tested that produced additive decrease in force (increase frequency) responses of oxytocin.

24.10

EFFECTS OF AN ADRENOCORTICOTROPIC HORMONE FRAGMENT, ACTH (4-10), ON ANGIOTENSIN CONVERTING ENZYME (ACE) AND ANGIOTENSIN II (AII) RESPONSES IN ISOLATED GUINEA PIG ILEUM AND RABBIT AORTA. Chau T. Huang and Richard H. Burns.* Norwich Eaton Pharmaceuticals, Inc., Norwich, NY 13815

We studied the effects of ACTH (4-10) on angiotensin I (AI), bradykinin (BK) and AII responses in isolated guinea pig ileum and rabbit aorta. In the guinea pig ileum, ACTH (4-10), like captopril and MK-421 diacid, inhibited AI (IC_{50}=8.0 μM), potentiated BK (AC_{50}=3.6 μM) responses, and had no effect on AII-induced contractions. In contrast, ACTH (4-10) potentiated the responses of rabbit aorta to AI by 23-35% at 1-3 μM, but slightly inhibited AI-induced contractions at 30 μM. In this tissue, ACTH (4-10) potentiated AII-induced contractions (AC_{50}=2.1 μM). This potentiating effect was blocked by verapamil (3 μM) and low calcium medium (0.4 mM). ACTH (4-10) showed no direct effect on the isolated rabbit aorta at concentrations up to 5 μM. In guinea pig ileum, on the other hand, ACTH (4-10) produced concentration-dependent contractile responses by itself (1-30 μM). Thus, although ACTH (4-10) appears to possess ACE inhibiting activity in both tissues, its actions in the aorta differs in that it potentiates the AII responses and produces no direct effect by itself.

LUNG GENERAL AND METABOLISM

25.1

TEMPERATURE AND POSTURE EFFECTS ON LUNG VOLUMES DURING PROLONGED EXERCISE. J.R. Wilson*, W.E. Sinning* and D.T. Deutsch* Applied Physiology Research Laboratory, Kent State University, Kent, Ohio. (Sponsored by P.B. Raven)

12 males (22-37 years) exercised for 60 min in hot [(H) 30°C DB, rh 70%] and cold [(C) 5°C DB, rh 37%] conditions in supine (S) and upright (U) positions to determine whether changes in lung volumes during exercise were related to changes in central blood volume (CBV). It was hypothesized that changes in total lung capacity (TLC) would be inversely related to changes in CBV indicators [cardiac output ($\dot{Q}$) and stroke volume (SV)] and directly related to an indicator of peripheral blood volume, forearm blood flow (FBF). TLC was higher for U than S (+469 ml), for H than C (+521 ml) and for exercise (Ex) than rest (Re) (+144 ml) with no interaction between conditions. Changes in forced vital capacity (FVC) paralleled changes in TLC (U/S, +388 ml; H/C, +600 ml; Ex/Re, +143 ml) while residual volume (RV) differences were nonsignificant. $\dot{Q}$ was higher in S than U at Re (+1.47 $l \cdot min^{-1}$) but not different due to Ex or temperature (Te) however, SV was lower in H than C (-73 ml), U than S (-18 ml) and Re than Ex (-16.4 ml) suggesting a reduced venous return and CBV under these conditions. FBF was higher in H than C and during Ex than Re (+2.21 and +4.08 ml·100 ml tissue-1) suggesting increased peripheral blood distribution. U and S differences were not significant. CBV and FBF changes were as hypothesized for Te and Ex suggesting CBV affects TLC by altering FVC.

25.2

EFFECT OF THEOPHYLINE ON INTRAPLEURAL PRESSURE OF VENTILATED GOLDEN HAMSTERS. J.M. Bell*, J.I. Klapper-Lehman* and L.N. Reinking. Millersville University, Millersville, PA 17551

Recent evidence has indicated that the main therapeutic benefit of theophyline is not bronchodilation but rather through an increase in the contractility of respiratory muscles. This study examines theophyline's influence on intrapleural pressure during mechanical ventilation prior to and after respiratory paralysis. Eight hamsters were anesthetized with Inactin (150 mg/kg); a plastic tube and a small volume of normal saline (1 ml) were introduced into the intrapleural space. Intrapleural pressure was recorded and theophyline (aminophylline, Abbott) was injected as a bolus (7.5 mg/kg) via the jugular. This injection was repeated after treatment with d-turbocurarine (1 mg/kg). Theophyline injections caused a significant and sustained increase in the magnitude of intrapleural pressure (p=.0001, ANCOVA). Pressure fell to or below pretreatment levels after injection of curarie. The second injection of theophyline had no effect. This study suggests that theophyline decreases pulmonary compliance and increases intrapleural pressure by potentiating muscle contractility. (Support: AHA, Lancaster Pa. Chapter)

25.3

THE EFFECT OF EXERCISE ON THE DEPOSITION AND RETENTION OF INHALED PARTICLES. W.D. Bennett*, M.S. Messina* and G.C. Smaldone. SUNY, Stony Brook, N.Y. 11794.

To investigate the effect of exercise and its associated increase in ventilation on the deposition and subsequent retention of inhaled particles, we measured the fractional and regional lung deposition of a radiolabelled (^{99m}Tc) monodisperse aerosol (2.6 um MMD) in normal, human subjects at rest and while exercising on a bicycle ergometer. Deposition fraction (DF) was measured by tyndallometry and gamma camera analysis was used to 1) determine the regional distribution of lung deposition and 2) monitor lung retention for 2½ hours ($R_{2½}$) and again at 24 hours (R_{24}). The product of DF and R_{24} gave a measure of fractional burden at 24 hours, B_{24} (the fraction of inhaled aerosol residing in the lungs 24 hours after exposure). We found that DF was unchanged between ventilation at rest (6-10 L/min) and exercise (32-46 L/min). Exercise caused a slight, but significant, increase in central, bronchial deposition. As a result, $R_{2½}$ and R_{24} were only mildly reduced following the exercise vs. resting exposure, but B_{24} was not significantly different between rest and exercise. Thus, total lung burden (B_{24} times the amount of aerosol inhaled)increased proportionally with the increased ventilation of exercise. Finally, for both rest and exercise, we found significant intersubject variability in B_{24} that correlated with intersubject variability in breathing pattern, i.e. tidal volume and breathing period. These results may be important in defining determinants of inhalation toxicity. NIEHS ES07088.

25.4

BRONCHOPULMONARY DISTRIBUTION OF A SALINE AEROSOL IN PATIENTS WITH ASTHMA AND IN NORMAL SUBJECTS. **Beth L. Laube*, David L. Swift* and G. K. Adams, III. JHU School of Medicine, The Good Samaritan Hospital, Baltimore, Md. 21239**

We studied bronchopulmonary distribution of a 0.9% saline aerosol (MMAD = 1.12 μm; σg = 2.04) labelled with ^{99m}Tc sulfur colloid in 10 asymptomatic asthma patients (AP) and 7 normal subjects (NS). An Ideal Medical raindrop nebulizer was used with a Nebulization-Dosimeter to deliver aerosol for 0.6 seconds at 50% vital capacity while subjects inhaled at 0.5 l/sec from residual volume to total lung capacity. Aerosol deposited in the bronchopulmonary region was quantified using a gamma camera. Percent bronchopulmonary clearance (an indirect measure of aerosol distribution) in AP ranged from 3.5 to 38.5 in 97 min. with a mean of 15.2 ± 12.6, and in NS from 0 to 10.5 with a mean of 6.5 ± 3.7, which were not statistically different (p = 0.261; Wilcoxon rank-sum test). Counts per picture element in an inner and outer zone of the right lung of AP were significantly different with 31.7 ± 13.2 and 23.0 ± 4.4 respectively (p = 0.012; Wilcoxon signed-rank test). Inner and outer zone counts for the NS were not different with 28.8 ± 7.4 and 26.9 ± 4.8 respectively (p = 0.173; Wilcoxon signed-rank test). These data suggest that bronchopulmonary deposition of aerosols is non-uniform in AP. This may contribute to the increased airway reactivity characteristic of AP, since non-uniform deposition of inhaled bronchospastic agents could result in focal regions of high drug concentration on the airway surface.

25.5

OZONE INDUCES LATE BRONCHIAL RESPONSES IN CONSCIOUS SHEEP. William M. Abraham, J.S. Stevenson*, G.A. Chapman*, L.D. Yerger*, E. Codias*, A. Hernandez*, and M.W. Sielczak*. U. Miami at Mt. Sinai Med. Center, Miami Beach, FL 33140.

Non-immunologic, as well as immunologic mast cell degranulation results in early and late increases in airflow resistance in conscious sheep. In this study, we determined if ozone (O_3), an oxidant pollutant which may also release mediators in the airways, would have the same effect. Specific lung resistance (SR_L) was measured before and at predetermined times after sheep (n=5) were exposed via their natural airways to either 1 ppm O_3 or filtered air (control) for 2 hrs. Neither O_3 nor air altered SR_L immediately after exposure. By 6.5 hrs, however, the O_3-exposed group had increases in SR_L, and SR_L remained elevated through 8 hrs. The average increase in SR_L during this time was 110% ($p<0.05$). Air exposure produced no such change. Effluents from bronchoalveolar lavage of the O_3 group tended to have more total cells with an increased proportion of macrophages, compared to controls. Lavage effluents from the O_3-exposed group also had increased amounts of the inflammatory mediator leukotriene B_4 (0.78 ng/ml) as measured by radioimmunoassay, compared to that previously found in normal lavage effluents (0.14 ng/ml; $p<0.05$). Therefore, O_3 induces late bronchial responses in sheep. These responses may be related to increased levels of inflammatory mediators released from activated cells. Supported by NIEHS-02668 and Merck Frosst.

25.6

PULMONARY BLOOD FLOW (Q) AFFECTS LUNG METABOLISM MEASUREMENTS. A.L. Harabin, L.D. Homer, E.T. Flynn*, M.E. Bradley. Naval Medical Research Institute, Bethesda, MD 20814.

Lung metabolism is commonly expressed as an extraction ratio(E=(PA-Ao)/Ao, where Ao=outflow substrate concentration, PA=inflow concentration) or as a concentration difference across the lung(Δ)(PA-Ao). In this presentation, we show that Ao reflects changes in Q independent of changes in enzyme activity per se, and the Q effects must be treated before altered lung enzyme capacity may be inferred. A metabolism model that includes both flow and concentration dependence (Bass et al., J Theor Biol 61: 393, 1978) predicts that when substrate concentration << Km

$$Ao = PA * e^{-Vmax/(Km*Q)}$$

where Vmax, Km=Michaelis Menten constants. E and Δ at a given Q are determined for each enzyme system by a characteristic Vmax/Km ratio. The model predicts that if Q alone increased by 50%, E would decrease 20 or 30% for systems with a control E of 0.8 or 0.2, respectively. Halving Q would increase E by 20 or 80%, respectively. Conversely, if metabolism is expressed in terms of Δ instead of % changes in E, the effects of Q could be more difficult to detect in systems of small control Δ. Because hypoxia increases Q 20 to 100%, changes in Q alone can explain some or all of the hypoxic depression of lung metabolism reported in the literature. (Supported by work unit M0099PN.01C.0010.)

25.7

PULMONARY METABOLISM OF ENKEPHALINS. P.A. Crooks*, J. Krechniak*, J.W. Olson*, R.J. Altiere*, and M.N. Gillespie*. (SPON: L. Diamond). Univ. of Kentucky College of Pharmacy, Lexington, KY 40536, Divisions of Medicinal Chemistry, and Pharmacology and Toxicology.

Pulmonary metabolism may be of significance in regulating systemic levels of Leu- and Met-enkephalin (LE and ME, respectively). To determine whether LE and ME are metabolized during passage through the pulmonary circulation, ^{3}H-Tyr-LE or ^{3}H-Tyr-ME (1 μM) were each administered to isolated, buffer perfused rat lungs and a newly developed high-pressure liquid radiochromatographic technique was used to identify and quantitate metabolic products. Both LE and ME were metabolized in a linear, time-dependent manner. The principal metabolites identified after 20 min of recirculating perfusion were expressed as a percentage of the total radioactivity at that time and were: Tyr (20% and 36% for LE and ME, respectively), and TyrGlyGly (39% for LE and 42% for ME). Residual LE and ME accounted for 28.4% and 14.3%, respectively, of the radioactivity present in each of the 20 min perfusates. Neither TyrGly nor TyrGlyGlyPhe were detected in significant amounts. The angiotensin converting enzyme (ACE) inhibitor, captopril (18 μM), blocked the formation of TyrGlyGly while having relatively less effect on the production of Tyr. These results indicate that at least two enzymes, ACE and an aminopeptidase, metabolize LE and ME during transit through the pulmonary circulation.

25.8

EFFECTS OF ASCORBIC ACID ON NITROFURANTOIN-INDUCED GLUTATHIONE OXIDATION IN ISOLATED, PERFUSED RABBIT LUNGS. Jacob R. Dunbar* and Anthony J. DeLucia. Quillen-Dishner College of Medicine, East Tennessee State University, Johnson City, TN 37614

We showed previously (Biochem. Pharmacol. 33:1343-1348, 1984) that perfusion of isolated rabbit lungs with nitrofurantoin (NF) or paraquat (PQ) results in a distinct alteration of glutathione redox (oxidized:reduced ratio). This change is probably secondary to NF- and PQ-stimulated production of superoxide and other oxidant species. Besides glutathione, other water-soluble antioxidants may be determinants of pulmonary oxidant toxicity. Therefore, in this study we have investigated the effects of exogenous ascorbic acid (AA) on NF-induced formation of oxidized glutathione (GSSG) in perfused rabbit lungs. Thirty minute perfusion of lungs with buffer containing 1 mM AA caused no detectable alteration in GSSG level or leakage of glutathione into the perfusate. 1 mM AA and 250 M NF resulted in elevation of lung GSSG levels to 14.3±3.7% of total intracellular glutathione (TG), compared to 8.0±0.5% of TG in lungs perfused with NF alone. GSSG content of control perfused lungs was only 0.8±0.6% of TG. GSH+GSSG efflux increased from 1.2±0.3% to 3.3±1.1% leakage with NF alone and 2.9±1.1% leakage with NF+AA. From the standpoint of glutathione redox alterations caused by NF, AA had a pro-oxidant, rather an antioxidant effect.

AGING, ENDOCRINOLOGY AND METABOLISM

26.1

EFFECTS OF AGING ON SERUM THYROXINE AND CORTISOL RESPONSES TO LOW AMBIENT TEMPERATURES IN THE DOG. D.L. Palazzolo* and S.K. Quadri. Kansas State Univ., Manhattan, KS 66506.

Effects of aging on serum thyroxine (T_4) and cortisol responses to cold stress have not been adequately investigated and what little information is available is contradictory. In the present study, the responses of these hormones were measured in young (2.5 yrs) and old (12.5 yrs) beagle dogs during a 5-hr exposure to 22° (control), 10°, and 4°C. Serum T_4 and cortisol were determined at 0, 0.5, 1, 2, 3.5 and 5 hrs during and at 1 and 3 hrs after the end of exposures. Basal serum T_4 levels in the young dogs (4.0 ± 0.4 μg/dl) were higher ($P < 0.05$) than those in the old dogs (2.5 ± 0.1 μg/dl). In the young dogs, exposure to 10°C produced increases ($P < 0.05$) in serum T_4 at 3.5 and 5 hrs. Exposure to 4°C raised serum T_4 at 3.5 and 5 hrs and the levels remained higher ($P < 0.025$) for 1 hour after the end of exposure. Unlike in the young dogs, cold exposure had no effect on serum T_4 in the old dogs. Basal levels of serum cortisol in the old dogs (20.9 ± 5.1 ng/ml) were higher than those in the young (18.3 ± 2.5 ng/ml) but the difference was not significant. In the young dogs exposure to 4°C produced a significant but temporary increase in serum cortisol at 1 hr, whereas exposures to 10° and 22°C had no effect. None of the three temperatures had any effect on serum cortisol in the old dogs.

These results indicate that aging affects serum T_4 and cortisol responses to cold stress.

26.2

CALMODULIN (CAM) LEVELS AND CALCIUM (CA^{2+}) STIMULATION OF ADENYLATE CYCLASE (AC) IN FRONTAL CORTEX AND HIPPOCAMPUS FROM PATIENTS WITH ALZHEIMERS DISEASE (AD). M. T. Piascik* and W. Markesbery* (SPON D. Randall), Dept. Pharmacology, Center on Aging, Univ. of Kentucky Medical Center, Lexington, KY 40536

The CAM levels and Ca^{2+} effect on AC activity were determined in postmortem specimens in frontal cortex and hippocampus from patients with AD and controls. CAM levels did not differ significantly in either frontal cortex (1222 ± 179 ng calmodulin/mg) or hippocampus (275 ± 101 ng/mg) from AD patients compared to control (1455 ± 418 ng/mg frontal cortex; 351 ± 127 ng/mg hippocampus). CAM levels associated with lysed synaptosomal membranes prepared from either frontal cortex (101 ± 9 ng/mg) or hippocampus (49 ± 13 ng/mg) from AD brain did not differ significantly from controls (232 ± 80 ng/mg frontal cortex; 45 ± 21 ng/mg hippocampus). AC activity associated with lysed synaptosomal membranes was stimulated then inhibited by Ca^{2+}. Values for one-half maximal stimulation and inhibition by Ca^{2+} did not differ significantly for any synaptosomal preparations. Ca^{2+} activation of AC from AD frontal cortex was significantly reduced when compared to control. Neither Ca^{2+} dependent inhibition of AC from AD frontal cortex nor stimulation or inhibition of AC from AD hippocampus differed from control. These data suggest: 1) There is no significant difference in CAM levels of frontal cortex or hippocampus in AD when compared to controls. 2) A decrease in responsivity of AC to Ca^{2+} is associated with AD in frontal cortex but not hippocampus. (Supported by PMAF and NIH Grant AG02759.

26.3

Cardiovascular Fundtion During Sleep in Older Adults and the Effects of Exercise. Wendy C. Bevier, David E. Bunnell*, and Steven M. Horvath. Institute of Environmental Stress, UCSB, Santa Barbara, CA 93106.

Sleep patterns of individuals change with advancing age and mechanisms responsible have not been explicated. Although some studies have reported on the electroencephalogram (EEG) sleep patterns of older adults few studies have simultaneously recorded nocturnal cardiovascular (CV) function. To establish a relationship between EEG and CV changes over the night 14 elderly subjects (57-72 yrs) were studied on five consecutive nights. EEG, electrooculogram (EOG), and electromuogram (EMG) were recorded by standard methods. The CV system was monitored using impedance cardiography. The adaptation night was followed by two baseline nights (B). On the afternoon of the fourth night (E) subjects walked for one hour at 60% of their $\dot{V}O_2max$. The fifth night was a recovery night. The typical pattern of heart rate (HR) decline over the night seen in young subjects was absent on B & R nights in older subjects. Although HRs were higher throughout the entire E night, a decline was seen. As in young subjects cardiac output (CO) and stroke volume (SV) declined across the night, reaching a low point 4-5 hrs after sleep onset on B & E nights. During E night CO-SV were lower, declined faster, and reached a low point sooner compared to B night values. The CO-SV pattern in older adults differed from an elevated pattern in young subjects after exercise. A disruption of circadian rhythms or a change in CV system sensitivity may be causative factors.

26.4

SENESCENCE IN SMALL POPULATIONS: APPLICATION TO APLYSIA. H. R. Hirsch and B. Peretz. Dept. of Physiology and Biophysics, U. of Kentucky, Lexington, KY 40536-0084.

Two problems arise in studying natural mortality in the laboratory: (1) It is often impractical to maintain an isolated population solely for this purpose, and (2) the number of animals is usually small. Useful approaches to these problems were developed in the course of an experiment in which the postmetamorphic age at death was calculated from the shell diameters of 112 Aplysia californica that died of natural causes. The median age at death was 155 days. The animals were a subpopulation of approximately 600 Aplysia that were maintained for sacrifice in other experiments. Our calculations support the validity of an actuarial separation of the subpopulation if animals chosen for sacrifice are selected solely on the basis of age. Senescence was demonstrated by a monotonic rise in the age-specific mortality rate. Statistical fluctuation, important because of the small population size, was reduced by grouping the data in bins containing approximately equal numbers of deaths rather than in bins of equal age increment. We show that the number of bins should approximate the cube root of the population size. Gompertz and power laws fit the experimental age-specific mortality-rate function equally well. Since Aplysia grow linearly throughout their lifespan, their senescence indicates that aging is not the result of the cessation of growth. (NIMH, NIH).

26.5

COMPARATIVE RESPONSIVENESS OF MALE AND FEMALE RAT ADRENALS TO ACTH BY COLUMN PERFUSION AND ISOLATED CELL INCUBATION. David Magrane* (SPON: D.M. Miller). Morehead State University, Morehead, KY 40351

Conditions for optimal response to exogenous ACTH in rat adrenals were evaluated by column perfusion of quartered rat adrenals and by incubation of intact cells isolated by the collagenase method. To obtain consistant basal release of corticoids, rats were maintained under standardized conditions with minimal disturbance. They were stunned, decapitated, and their adrenals removed as quickly as possible. It was found that a 1 hour preincubation period was required to obtain basal values of corticoid release. Only these conditions gave maximal tissue responsiveness to low doses of ACTH with column perfusion, suggesting elimination of residual effects of bound endogenous ACTH. The LD_{50} response for rats was about 5 mU ACTH/ml/2 adrenals; (flow rate, 0.7 ml/min). Adrenals from male and female Sprague Dawley rats were perfused at prepuberal, postpuberal, and adult stages. Significant differences in adrenal weight and ACTH response(stimulated over basal corticoid release) were apparent after postnatal day 40. Adult male response per mg of tissue exceeded females by 50%: however, response per pair of adrenals was the same between sexes. These same differences were not observed in the isolated cell preparations. The LD_{50} response in isolated cells (40×10^4 cells/adrenal/ml) was 0.01 mU ACTH/ml. Comparison of cAMP and pregnenolone following ACTH stmulation also revealed no differences between isolated cells of males and females.

26.6

RELATIONSHIP BETWEEN MALE SEXUAL BEHAVIOR AND SIZE OF THE SEXUALLY DIMORPHIC NUCLEUS (SDN) OF THE PREOPTIC AREA OF THE HYPOTHALAMUS IN MALE RATS. R.W. Rhees, R.H. Anderson* and D.E. Fleming. Departments of Zoology and Psychology, Brigham Young University, Provo, 84602

The Sexually Dimorphic Nucleus (SDN) within the medial preoptic area of the hypothalamus is several times larger in adult male rats than in adult females. Previous research has shown that prenatal stress has a demasculinizing effect on male sexual behavior. The present study was designed to test a possible relationship between the size of the SDN and sexual activity in adult male control and prenatally stressed rats. Stress consisting of immobilization, illumination, and heat was administered three times daily in the third trimester of pregnancy (days 14-20). Male offspring were tested for sexual activity for seven consecutive weeks. The male offspring were then sacrificed and the brains were fixed, sectioned at 50 microns, and stained with thionin. The cross-sectional area of the SDN was identified with light microscopy and the volume of the SDN was determined by tracing magnified serial sections of the area with a planimeter. The data confirm previous reports that prenatal stress significantly reduces the size of the SDN compared to control animals. However, the SDN volumes of sexually active animals of both stress and control groups were approximately equal in size and were two times larger than sexually nonactive animals of either group. These data suggest that male sexual activity is correlated with the size of the Sexually Dimorphic Nucleus.

26.7

NEUTRAL AMINO ACID UPTAKE SYSTEMS IN RABBIT BLASTOCYSTS. J. Bell*, K. Begg*, J. Biggers, D. Benos Laboratory of Human Reproduction and Reproductive Biology, Harvard Medical School, Boston, MA 02115.

The presence of the amino acid uptake systems A, ASC, and L was determined in 6 day old rabbit blastocysts from the dependence of aminoisobutyric acid (AIB) tissue uptake on $[Na^+]$ and by the inhibition of uptake by system specific amino acid analogues MeAIB (methylaminoisobutyric acid, A system) and BCH (2-aminobycyclo-[2,2,1]-heptane-2-carboxylic acid, L system). At 0.5 mM external AIB blastocysts had an intial rate of AIB uptake of 0.44 + 0.04 nmoles cm^{-2} hr^{-1} (N = 12). Approximately 70% of this flux occurred through the ASC system as defined by its Na^+ dependency and lack of inhibition by 25 mM MeAIB; 20% of the flux was not affected by Na^+ removal nor was inhibited by 10 mM BCH and thus considered to enter through system L. The remaining 10% appeared to be a nonsaturable component (NS). MeAIB was used as a substrate to assay the operation of the A system. The initial rate of MeAIB uptake was low, (with an upper limit of 0.02 nmoles cm^{-2} hr^{-1}) and was not affected either by reducing external $[Na^+]$ or by the addition of BCH. MeAIB uptake was measured in 5 and 7 day blastocysts as well, and showed similar rates and properties as in the 6 day blastocysts. We conclude that systems ASC and L are operative in the day 6 blastocyst and that the A system is not a major contributor to amino acid uptake in day 5-7 blastocysts. This work was supported by NIH Grants HD 12353 and by T32HD07130.

26.8

EFFECT OF PHENOXYBENZAMINE (POBZ) ON PLACENTAL BLOOD FLOW IN DIET RESTRICTED, TERM-PREGNANT RATS. R.A. Ahokas, S.L. Reynolds*, G.D. Anderson*, and J. Lipshitz*. Univ. of Tenn. Ctr. Hlth. Sci., Memphis, TN. 38163.

We have previously shown that dietary restriction throughout pregnancy causes fetal growth retardation and a 50% reduction in placental blood flow (PBF) at term in the rat. The objective of this study was to determine if the lower PBF was the result of increased α-adrenergic vasomotor tone. Maternal cardiac output (CO), and PBF were measured in anesthetized (Na pentobarbital, 35 mg/kg, ip) term-pregnant rats, 1.) fed ad libitum (N=8), and 2.) and fed 50% of the average daily amount of food consumed by the ad libitum fed rats (N=8), with 15 μm, radiolabeled microspheres. POBZ was administered (3 mg/kg, ip), and 60 min later CO and PBF were measured again with differently labeled microspheres. Mean femoral arterial blood pressure (MAP) was measured prior to each CO and PBF determination. PBF was lower in the malnourished rats than in the ad libitum fed rats before POBZ administration. POBZ decreased MAP in both groups of rats, but had no effect on CO. Placental vascular resistance (PVR) was decreased by POBZ in the malnourished rats; PBF was unchanged. In the ad libitum fed rats POBZ had no effect on PVR and PBF was significantly reduced. The results indicate that the lower PBF associated with malnutrition is the result of increased α-adrenergic vasomotor tone, providing additional evidence that mother actively limits the supply of nutrients available for placental transfer to the fetus during malnutrition.

26.9

PLASMA Δ-9-TETRAHYDROCANNABINOL (THC) LEVELS IN PREGNANT SHEEP AND FETUS AFTER SMOKING A MARIJUANA CIGARETTE.
R. Abrams, C. Cook*, K. Davis*, K. Niederreither*, M. Jaeger and H. Szeto*. Depts. of Ob-Gyn and Physiol, Univ. of Florida Med. Ctr., Gainesville, FL 32610, Research Triangle Inst., NC, and Dept. Pharmacol., Cornell Univ. Med. Ctr., NY.

Five pregnant ewes with gestation dates of 128-142 days were prepared surgically with catheters in maternal femoral artery and fetal subclavian artery or fetal superior vena cava. A silicone rubber T tube was placed in maternal trachea. One marijuana cigarette (3.19% THC) was burned continuously for 8-10 min in a lightweight smoking machine attached to the ewe. Air flow rate through cigarette was 150 ml/min. Smoke was inspired through the open-ended tracheostomy tube. Samples of blood were taken at 3,6,10,15,30,60,90 min and 3,4,6,12,24 hr. Highest maternal plasma THC (mean: 120 ng/ml) was found in the 10 min sample at which time detectable amounts of THC were found in the plasma of 3 of 5 fetuses. Highest values of fetal THC (mean: 8 ng/ml) were achieved in samples between 1.5 - 4 hr. The ratio of fetal to maternal THC levels between 1.5 - 12 hr averages 0.46. THC was detected in 1 of 5 fetuses 24 hr after maternal smoking of one marijuana cigarette. (Marijuana cigarettes supplied by The National Institute on Drug Abuse).

26.10

CHOLERA TOXIN ENHANCED DEVELOPMENT OF BALB/C MOUSE MAMMARY GLANDS IN VIVO. L.G. Sheffield* and C.W. Welsch. Michigan State University, East Lansing, MI 48824.

Cholera toxin (CT), a potent stimulator of intracellular cAMP, increases growth of normal mammary epithelia in vitro. No studies have been reported on the effect of CT in vivo on normal mammary development and growth. In order to test the mammogenic effect of CT in vivo, CT (0.1 µg/day) and/or 17ß-estradiol (1.0 µg/day) + progesterone (1.0 mg/day) (E/P) were injected s.c. into 4-month old intact and ovariectomized female Balb/c mice for 20 days (10 mice per treatment). Mammary glands were removed, stained, and mammae development graded on a scale of 1 to 6 (6 representing maximum development, as in late pregnancy). Mammary development scores were as follows:

	Control	CT	E/P	CT+E/P
Intact	2.0±.08	3.6±.20	4.1±.10	5.2±.10
Ovariectomized	2.0±.05	1.9±.10	3.2±.15	4.0±.10

In intact mice, CT significantly ($P<0.05$) increased ductal/alveolar development with or without administered E/P. In ovariectomized mice, CT significantly ($P<0.05$) increased ductal/alveolar development in the presence of E/P, but in the absence of E/P, CT was without an effect. Thus, chronic administration of CT to female Balb/c mice causes a striking increase in mammae development, an effect contingent upon the presence of ovarian steroids. (Supported by NIH-HD-17331).

26.11

THE EFFECTS OF HEAT STRESS ON PLASMA CATECHOLAMINES IN THE DOG. D.C. McKell* and S.K. Quadri, Kansas State Univ., Manhattan, KS 66506.

Little or no information is available on the effects of high ambient temperature on plasma catecholamines (CA) although a few reports on tissue CA concentrations have appeared. In this study electrochemical high performance liquid chromatography was used to measure plasma levels of epinephrine (E), norepinephrine (NE) and dompamine (D) 7 times during an 11-hour exposure of 2-month old beagle dogs to either 22°, 29°, 35° or 41°C at ventilation rates of 8%, 16% or 32%. Relative humidity (50%) and air-flow rate (110 fpm) were kept constant. Exposures to 22°, 29° and 35°C produced no significant changes in basal concentrations of E(282.3 ± 15.8 pg/ml) or NE(636.6 ± 25.8 pg/ml). Exposure to 41°C produced a 5-fold increase in plasma E and a 3-fold increase in NE within 3 hrs. However, both E & NE returned to basal levels by the 8th hr and remained there during the remaining 3 hrs of exposure. Ventilation rate had no effect. E and NE levels in 2 daily blood samples before the exposure were not different from those in two daily blood samples after the exposure indicating that exposure to high ambient temperatures produced no permanent change in CA synthesis and release mechanisms. DA levels remained undetectable.

These results indicate that except for a transient increase at 41°C, plasma CA levels remain unaffected during exposure to high ambient temperatures.

26.12

INTERMEDIATE LOBE PEPTIDES IN BOVINE PITUITARY INTRAGLANDULAR COLLOID. William H. Boyd. Biomedical Sciences, Univ. of Guelph, Guelph, Ontario. N1G 2W1

Peptides αMSH, ACTH and βLPH synthetized by cells in the pituitary intermediate lobe have been discovered in bovine pituitary intraglandular colloid (IGC) following its subjection to a series of radioimmunoassays (RIA) including αMSH-RIA, ACTH-RIA and βLPH-RIA. Bovine IGC, the holocrine secretion of intermediate lobe cells housed in the intraglandular lumen (residual lumen) was collected 5 min after slaughter, placed in a mixture of 1.0 N HCl, 1.0 M acetic acid, 1% NaCl, allowed to precipitate in the cold for 2 h, then centrifuged at 15 K rpm for 30 min at 4°. The supernatant was passed through a Sep-Pak C_{18} cartridge. The cartridge was washed and the peptides retained were eluted with 3 ml of 80% acetonitrile with 0.1% TFA. The eluent was freeze dried, the powder weighed and dissolved in 2.5 ml of cold 0.01 HCl and 0.1% BSA. RIA was performed on this material. IGC thought to be the transport medium for intermediate lobe hormones with accessions from the anterior lobe of the gland, gains the systemic circulation of the cavernous sinuses via clefts within the capsule of the gland aligned with the intraglandular lumen. The lumen also opens into the subarachnoid CSF space via well defined channels and clefts surrounding the hypophyseal stalk. Since the intermediate lobe is poorly vascularized, the channels and clefts provide the most efficient entrance of intermediate lobe materials into the systemic circulation and CSF. Supported by NSERC Canada.

26.13

THE EFFECT OF GNRH AND E_2 ON THE INCORPORATION OF GALACTOSE, MANNOSE AND SULFATE INTO RAT LH. **J.W. Ramey*, W.W. Wilfinger*, R.F. Highsmith and D.M. Baldwin, Dept. Physiology & Biophysics, Univ. Cinti. Med. Coll., Cinti., OH 45267**

Previous studies from our laboratory have shown that GnRH stimulates the incorporation of ^{3}H-glucosamine into LH with no effect on amino acid incorporation. Estradiol (E_2) enhances this GnRH-stimulated response. The purpose of this study was to evaluate the effects of E_2 and GnRH on the incorporation of mannose, galactose and sulfate into immunoprecipitable LH. Anterior pituitary cells from random cycling female rats were initially cultured for 48h in steroid-free, α-modified Eagles medium + charcoal stripped horse serum before being incubated for 24h in control or E_2 (0.5 nM) supplemented medium. The cells were then incubated (4h) with fresh medium containing ^{3}H-galactose, ^{3}H-mannose, or ^{35}S-sulfate (30 µc/ml) +/- 1 nM GnRH (5 replicates/treatment). Radiolabeled LH in cells and medium was determined by immunoprecipitation. GnRH enhanced the incorporation of ^{3}H-galactose into LH in the absence of E_2, whereas it had no effect in the presence of E_2. ^{3}H-galactose incorporation was not affected by E_2 alone. Neither GnRH or E_2 altered the amount of ^{3}H-mannose or ^{35}S-sulfate incorporated into LH. The amount of radioactively-labeled LH was always greater in the medium versus the cell extract. Based upon these results and previous data, we conclude that newly synthesized or processed LH is readily released and that the incorporation of various oligosaccharide constituents of the LH molecule are differentially regulated by GnRH and E_2. Supported by NIH 16994.

26.14

INHIBITION OF COPULATORY BEHAVIOR IN FEMALE RATS TREATED WITH ATROPINE. Tatiana Perez-Altamirano*, Syed Saiduddin and John J. Curry. The Ohio State Univ., Columbus, OH 43210

Previous studies have shown that cycling female rats treated with the cholinergic receptor blocker, atropine sulfate, fail to mate when placed overnight with stud males. Therefore, the effects of atropine upon the lordosis quotient (LQ) were studied in ovariectomized rats bearing estradiol-containing silastic capsules before, and fifteen minutes following administration of one of several doses of atropine sulfate. The pre-injection and post-injection LQ's (Mean±SEM) for each dosage group are shown in the following table:

DOSE OF ATROPINE (mg/kg Body Weight; i.p.)

	15	25	50	70
LQ Before Atropine	0.76 ±0.024	0.76 ±0.081	0.80 ±0.032	0.74 ±0.025
LQ After Atropine	0.32 ±0.097	0.10 ±0.100	0 -	0 -

The differences between pre-injection and post-injection values were statistically significant at all doses tested, however, a clear dose-response relationship was apparent. Animals treated with low doses of atropine displayed mild lordosis only after several mounts whereas those treated with higher doses (>50mg/kg) never displayed lordosis. In addition, aspects of proceptive behavior (ear-wiggling, darting-hopping) were often not curtailed at doses which impaired receptive behavior. These results suggest that cholinergic pathways may mediate at least the receptive component of copulatory behavior in the female.

26.15

GEOGRAPHIC DISTRIBUTION AND COPULATION INFLUENCE OVULATION RATE IN THE COTTON RAT (SIGMODON HISPIDUS). C. Oswald*and P.A. McClure* (SPON: H.D. Prange). University of Indiana, Bloomington, IN 47405

Litter size in many mammals increases with latitude. This investigation tested the hypothesis that geographic variation in litter size is the result of differences in ovulation rate. Oviducts and uteri of virgin, lab-reared descendants of cotton rats from Kansas (KSh), Texas (HSh), and Tennessee (TSh) were flushed on the day following the last day of estrus. The numbers of ova released differed significantly among the 3 populations($\bar{x} \pm$ SE KSh = 5.3 ± .3, HSh = 4.9 ± .6, TSh = 4.0 ± .5, $p < .1$). Because these ovulation rates for KSh and HSh are slightly lower than actual litter sizes in the lab and field, ova counts were also performed on rats within 24h after copulation. Ova counts for these animals were significantly different from each other ($p < .01$) and, for KSh and HSh, were significantly higher than in virgin females (KSh = 6.5 ± .3, HSh = 5.5 ± .9, $p < .1$). These ovulation rates agree more closely with litter size data. 85% of animals with high ovulation rates released ova from both ovaries while only 37% of those with low ovulation rates ovulated from both ovaries. Conclusions: Geographic variation in litter size in the cotton rat results from differences in ovulation rate. The number of ova released is influenced by the number of ovaries ovulating. Copulation can increase the number of ova released. This study supported in part by NIH grant 5 R01 HD 13953-02,03.

26.16

IN VIVO DELIVERY OF TESTOSTERONE BY ALCAP CERAMICS. M. A. McGuire* and P.K. Bajpai. University of Dayton, Dayton, OH 45469

Preliminary in vitro studies conducted with ^{3}H-progesterone release by hollow cylinders of aluminum-calcium-phosphorous oxides (ALCAP) indicated that this device was capable of delivering steroids. Further studies with an accelerated in vitro system demonstrated that high density ALCAP cylinders coated with polymer were capable of delivering testosterone (T) 28 days. Male albino rats weighing 325-375 g were used to study in vivo T release by ALCAP cylinders. Rats with intraperitoneal depots of T in oil served as comparative controls. High density ALCAP ceramics weighing 0.75 g were coated with polymer, filled with 45 mg T plus 0.5 μCi ^{3}H-T, sealed, and implanted intraperitoneally in 6 rats. Six rats received intraperitoneal injections of 0.3 ml oil with 45 mg T plus 0.5 μCi ^{3}H-T. Six uninjected rats served as normal controls. Rats were bled by the tail artery days 1 through 7, 14, and 28 after initiation of injection and implantation of T. Serum lipids were extracted from blood samples and counted by liquid scintillation. Rats injected with the oil depot showed detectable serum ^{3}H-T by day 3 after injection and none was detectable by day 28. Delivery of T was detected 5 days after implantation in rats with ALCAP cylinders. By day 14, a daily release of approximately 0.25 mg T per day per rat was recorded. This release rate did not vary by day 28. These data suggest ALCAP ceramics may be a viable material for sustained controlled delivery of steroids.

26.17

THE RELATIONSHIP BETWEEN THYROID HORMONES, CATECHOLAMINES AND CARDIAC DYNAMICS. Donna Van Wynsberghe and Laurel Rudolph.* University of Wisconsin, Milwaukee, WI 53201

Altered thyroid states were induced in adult male rats by subcutaneous injections of triiodothyronine (T_3) (1.5 mg/Kg) and its acetic acid analogue triiodothyroacetic acid (T_3AC) (1.5 mg/Kg). Plasma T_4, T_3 and catecholamines were determined. Right vagal bradycardia was induced in each group with a 2 volt, 6 sec stimulation. Selected cardiovascular parameters (heart rate, pulse pressure and mean arterial blood pressure) were determined during i.v. infusions of epinephrine and norepinephrine at low and high doses (0.0025 and 0.0050 mg/Kg). T_3 and T_3AC treatment reduced epinephrine and dopamine levels, resulting in an inverse relationship between circulating hormones and catecholamines. The magnitude of right vagal bradycardia was reduced with T_3 and T_3AC treatment. T_3 reduced heart rate by 25 b/min, and T_3AC, 28 b/min in comparison to 60 b/min for controls. Intravenous infusions of epinephrine and norepinephrine to T_3 and T_3AC treated rats resulted in similar cardiovascular responses as controls, indicating that the reduced circulating catecholamines and/or altered thyroid hormone levels may have altered the myocardial B receptor density and/or sensitivity.

26.18

THE EFFECTS OF ALTERED THYROID STATES ON CATECHOLAMINES IN YOUNG RATS. Carla Keller*, Donna Van Wynsberghe, and Anna Stadnicka, University of Wisconsin-Milwaukee, WI 53201

Hypothyroidism was induced in neonatal Sprague-Dawley rats by s.c. injection of 100-150 uCi of 131-I on day one of life. Chronic hyperthroidism was induced in littermates by daily s.c. injections of 1.0ug T3/10 g body weight, beginning on the fifth day of life. All littermates were sacrificed by decapitation on day 28 or 29. The catecholamine content of homogenates of entire adrenal glands was analyzed by HPLC with ECD; plasma levels of dopamine, norepinephrine, and epinephrine were analyzed by the same method.

In the T_3-treated rats, adrenal norepinephrine was significantly reduced, compared to the controls and hypothyroid rats. Adrenal epinephrine and dopamine levels were not significantly different between the three experimental groups. The percentages of total catecholamine content for norepinephrine (N), epinephrine (E), and dopamine (D) in the left adrenal for the control, T_3-treated, and hypothyroid rats are:

	N	E	D
C	17.0%	82.0%	1.0%
T_3	11.8%	86.7%	1.5%
131-I	16.3%	82.6%	1.1%

These data indicate that in young rats, as has been shown in adults, hyperthyroidism is associated with a decreased adrenal norepinephrine content, while adrenal epinephrine may remain relatively unchanged.

26.19

CORRECTION FOR ISOTOPE DILUTION IN MEASUREMENTS OF GLUCONEOGENESIS FROM THREE CARBON PRECURSORS. Joanne K. Kelleher* (Spon: R. A. Kenney). George Washington Univ. Medical Center Washington, D. C. 20037

When the rate of gluconeogenesis is estimated from steady state incorporation of 3 carbon precursors (e.g. alanine) into glucose, the following expressions is used:

$$\text{rate of gluconeogenesis} = \frac{\text{rate of labeling of glucose C\#1,2\&3}}{(\text{SA 3 carbon precursor}) \times d}$$

where d equals isotope dilution of the 3 carbon precursor. Hetenyi (1979) proposed that $d = 2y/(1+2y)$; the value of y is obtained from the glucose labeling ratio of Weinman etal. (1957). I suggest an alternative method for calculating d which includes the effects of the following 3 pathways on isotope dilution: (1) flux of 3 carbon precursor to the OAA pool via citrate carbons 4 & 5; (2) flux of 4 or 5 carbon compounds into the TCA cycle; (3) reversible flux between OAA and pyruvate, and between OAA and fumarate. Investigators can determine if these pathways are significant in a specific steady state system by the following 3 tests: Pathway 1 is significant if SA citrate C#4+5/C#2+3> 0 using either [2,3-^{14}C] or [U-^{14}C] alanine as tracer. Significance of pathway 2 is reflected in the SA of citrate C#2+3 using these tracers. Pathway 3 is significant if SA glucose C#1/C#3 > 1.0 using [U-^{14}C] alanine as tracer. If flux through these pathways is significant, use of Hetenyi's correction factor is inadequate for accurate estimates of gluconeogenesis. (Supported by NIH 5 SO1-RR-5359-22)

26.20

THE EFFECTS OF LOCAL AND SYSTEMIC INFECTION ON OXYGEN UPTAKE AND CORE TEMPERATURE IN THE BURNED RAT. L.H. Aulick, A.D. Mason, Jr.*, A.T. McManus and B.A. Pruitt, Jr.*, USAISR, Fort Sam Houston, TX 78234.

Resting oxygen uptake (VO_2) and colonic temperatures (Tc) were measured in groups of 400-500 gm, male rats (30/group) at thermoneutrality, before and for 21 days after 30% total body surface, full thickness burns. Burns were divided into three bacteremic (B) and five non-bacteremic groups. One of the latter groups was untreated (UT), two had wounds seeded with non-virulent Pseudomonas aeruginosa (NVP), and two had seeded wounds treated with Sulfamylon antimicrobial cream (NVPS). Controls (C) included a normal and a shaved group.

Group	(N)	VO_2 (ml/hr/gm) Before	VO_2 (ml/hr/gm) After	Tc (^{0}C) Before	Tc (^{0}C) After
B	(3)	0.83 ± .01	1.20 ± .01	36.8 ± .2	37.7 ± .1
UT	(1)	0.82	0.90	37.3 ± .1	38.0 ± .1
NVP	(2)	0.84 ± .00	1.03 ± .01	37.1 ± .0	37.8 ± .1
NVPS	(2)	0.81 ± .01	0.95 ± .02	37.0 ± .2	37.6 ± .1
C	(2)	0.78 ± .02	0.77 ± .01	36.8 ± .1	36.8 ± .1

(Mean ± SE, N = Number of Groups)

Tc increased to the same general level in all burn groups. Localized wound contamination (NVP) and systemic infection (B) raised VO_2 above that caused by burn alone (UT). Sulfamylon attenuated bacterial effects (NVPS), but the data suggest that bacteria in the wound can amplify postburn hypermetabolism.

26.21

MITOCHONDRIAL AUTONOMY DURING PROLONGED HYPOXIA. Robert E. Kuttner. Surg. Res. Lab., VA Med. Ctr., N. Chicago, Il 60064

Relative mitochondrial invulnerability is shown by the fact that only osmotic damage imperils function during the many preparative procedures in current use. Liver homogenates from the same 80-100 g rats (N=5) in either 95% oxygenated or aerated 0.25 M sucrose media yield similar ATP concentrations (6.4 ± 0.8 nmol/mg protein) for fed animals. The common finding that depressed mitochondrial energy production is minor or occurs late (12-18 h) in animals exposed to hypoxic episodes in different hemorrhagic or septic shock models is further evidence of well-maintained structural integrity (e.g. Schumer et al. Ann. Surg. 171:875, 1970). An explanation is needed for the paradox of an aerobic organelle with better resistance to hypoxia than the anaerobic cytosol compartment which suffers early metabolic derangement (kuttner et al. Adv. Shock Res. 4:73, 1980). It is argued that the mitochondrion is a slave organelle, originally an aerobic endosymbiont, totally specialized to produce ATP for predominantly extramitochondrial purposes. In exchange, other cell components assume the burden of synthesizing 95% of mitochondrial protein. Hypoxia denies mitochondrial ATP to the cytosol but does not increase hepatic mitochondrial energy needs until late shock phases when ammonia from peripheral protein degradation begins to arrive and requires ATP for citrulline formation.

(Aided by the VA Med. Res. Service).

26.22

THROMBOXANE A_2 AND PROSTACYCLIN SYNTHESIS IN PIGEONS OF DIFFERENT SUSCEPTIBILITY TO ATHEROSCLEROSIS. DAVID J. SAXON and JANET M. ROYER*. MOREHEAD STATE UNIVERSITY, MOREHEAD, KY 40351

Interaction of prostacyclin (PGI_2) and thromboxane A_2(TXA_2), two antagonistic metabolites of the arachidonic acid (AA) cascade, is necessary for maintaining vascular homestasis. This study was conducted to investigate the possible roles of TXA_2 and PGI_2 in susceptibility to atherosclerosis. Radioimmunoassay (RIA) was used to determine TXA_2 and PGI_2 levels in a strain of White Carneau (WC II) pigeons genetically very susceptible to atherosclerosis and another strain of random bred White Carneau (RBWC) genetically less susceptible to the disorder. Thromboxane B_2 ($TXB)_2$) and 6-keto-prostaglandin $F_1\alpha$ (6-keto-$PGF_1\alpha$), stable metabolites of TXA_2 and PGI_2, were measured by RIA as indicators for TXA_2 and PGI_2. Plasma and aorta samples were analyzed for 6-keto-$PGF_1\alpha$. Plasma and platelet rich plasma (PRP) were tested for TXB_2. RIA determinations for platelets and aorta included incubation with and without AA. The ratios of 6-keto-$PGF_1\alpha$ /TXB_2 were analyzed ANOVA. The less susceptible RBWC pigeons had significantly higher ratios of 6-keto-$PGF_1\alpha$/TXB_2 than the more susceptible WC II.

26.23

BILE ACID METABOLISM IN PREGNANCY: EFFECT OF CHOLESTYRAMINE ON BILE ACID METABOLISM IN THE PREGNANT RAT. Aslam S. Hassan and Judy J. Hackley*. Univ. of Illinois, Urbana,IL. 61801.

Cholestyramine(CTR), a non-absorbable anion exchange resin binds bile acids in the intestinal lumen and enhances the fecal excretion of bile acids. Typically, CTR treatment enhances the activity of hepatic cholesterol 7 alpha hydroxylase (CH-7A), the rate-limiting enzyme of bile acid biosynthesis. Recently, Innis found that pregnant rats fed 5% CTR (as Questran^R) did not show an increase in CH-7A activity (Am. J. Obstet. Gynecol. 146:13-16, 1983). Non-pregnant female rats treated with a similar level of CTR, however, showed a 3-fold increase in CH-7A activity. Since Questran is ca. 56% sucrose, and since the control pregnant animals were fed standard rat chow only, the difference in response to CTR vis-a-vis gestational status may have been due to the sucrose contents of the diets. We have investigated the effect of CTR alone on bile acid metabolism in the pregnant rat. Timed pregnant rats (8 days) were fed ground rat chow with or without 4% CTR. On day 20 of gestation, the rats were killed by exsanguination under anesthesia and the liver removed for CH-7A assay. While CTR treatment did not affect plasma cholesterol, CH-7A activity was significantly increased in the animals fed CTR (pmoles/mg·min, Mean ± SEM): Con (4) 14.7±1.7; CTR (4) 34.8±3.3, $p<0.005$. Our results suggest that CTR can affect bile acid metabolism in the pregnant rat.

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26.24

DIET VARIATION FAILS TO ALTER FOOD INTAKE(FI) IN LIVER DENERVATED(D) RATS. Fred E. Williams and Larry L. Bellinger. Baylor College of Dentistry, Dallas, TX 75246.

Liver glucoreceptor afferents have been proposed to provide a major influence upon FI control. Although previous attempts to demonstrate this control system by liver denervation(D) have failed, no variation in diet was tested. Female Sprague Dawley rats (225 gms) housed individually under a 12:12 L:D schedule with lights out at 13:00 hr were divided into 2 groups. Group 1 (n=12) were liver denervated by cutting all connections to the GI tract between the diaphragm and upper duodenum. The hepatic artery was removed, the portal vein and bile duct were stripped, and the vein treated with a 9% phenol:ethanol solution. Denervation was confirmed by H & E histology and catecholamine histofluorescence. Group 2 (n=15) were sham(S) operated. After recovery the two groups were given various test diets for 4-6 days with a 3-6 day period of chow between. The test diets were: 1.) chow plus 32% sucrose solution, 2.) 1:1 mixture of powdered chow and glucose, and 3.) 30% Crisco and powdered chow mixture. 24 hr FI was measured and corrected for spillage. Diet 1, day 1; sucrose (mls) S 30.1±1.3, D 24.3±1.9, t=2.3: chow (gms): S 8.7±0.7, D 9.0±0.7. 6 day means: sucrose, S 39.0± 1.3, D 33.2±2.9, chow; S 7.8±0.5, D 9.5±0.6. Diet 2: day 1, S 15.5±0.6, D 16.0±1.6. 4 day mean, S 16.0±0.3, D 16.1±0.7. Diet 3: day 1, S 13.3±0.5, D 14.9±0.9, t=1.63; 4 day mean S 14.8 ±0.5, D 15.7±0.6. These data do not support the liver glucoreceptor theory of FI. Supported by BCD research funds.

26.25

CHANGES IN RESPONSE PATTERNS OF RENAL ADRENOCEPTORS IN HIBERNATING VS ACTIVE GROUND SQUIRRELS. C.T. Harker, M.J. Kluger, R.L. Malvin, and C.E. Roast. Dept. of Physiology, The Univ. of Michigan Medical School, Ann Arbor, MI 48109.

Studies in this laboratory have shown that the response patterns of renal adrenoceptors to α- and ß-adrenergic drugs, as measured by changes in renin-release, are temperature-sensitive in the rat and dog. Does the chronic exposure to low core temperature seen in a hibernator induce changes in receptors that persist even when studied at temperatures found in normothermia? To test the hypothesis that changes in responsiveness to α- and ß-agonists occur in hibernation, cortical kidney slices from both hibernating (H) (13°C) and nonhibernating (NH) (37°C) Citellus tridecimlineatus were incubated in a physiologic salt solution at 37°C and stimulated with α- and ß-adrenergic drugs. The ß-agonist isoproterenol (10^{-5}M) caused a significant increase in the release of renin by slices taken from NH squirrels but had no effect on slices taken from H donors. Conversely, while the α-agonist phenylephrine (10^{-7}M) had no effect on tissues taken from NH squirrels, it caused a significant enhancement of renin-release by slices taken from H animals, thus providing evidence of direct stimulation of renin release by an α-agonist. Experiments are in progress to compare and contrast the responses from tissue slices incubated at 13°C. Research supported by NSF PCM 8019709.

26.26

EFFECTS OF SMOKING AND/OR RESTRAINT ON METABOLIC RATE OF RATS. R.D. Fell, J. Shearn* and B.A. Stamford. Exercise Physiology Laboratory, Univ. of Louisville, Louisville, KY, 40292.

Animals were exposed to smoke during restraint on a smoking machine developed by the Tobacco and Health Research Inst., Lexington, KY. Rats were either smoke exposed (Sm) 10 min/day or sham restrained (Sh) 5 days/week for 6 weeks. Metabolic rate was measured by open circuit indirect calorimetry before and after smoke exposure or for similar periods of time in restraints. Food intake was reduced in Sm and Sh rats compared with cage controls (CC). This was observed only on treatment days. Body weight gain overall was lower and heart wt/body wt ratios were higher in both Sm and Sh animals compared to CC. Sm had significantly heavier adrenal glands than either Sh or CC rats, thus suggesting greater stress from smoking. O_2 uptake (VO_2) and CO_2 production (VCO_2) were elevated in both Sm and Sh rats. After smoking, however, VO_2 decreased significantly in Sm. VCO_2 increased after smoke exposure in Sm and restrained Sh animals. Restrained animals hyperventilated which prevented accurate calculation of caloric costs. In conclusion: (1) the stress of being restrained may be responsible for significantly elevating VO_2; (2) cigarette smoke exposure appears to decrease this level of stress. It remains to be determined in an animal model whether or not cigarette smoke effects metabolic rate by means other than simply reducing caloric intake. (Supported by a grant from the Tobacco and Health Research Institute).

27.1

CONVECTIVE INTERREGIONAL MIXING DURING HIGH FREQUENCY OSCILLATION (HFO). K.S. Kapitan,* M.D. Hammond* and J.B. West. Department of Medicine, University of California, San Diego, La Jolla, California 92093

Rapid interregional gas mixing during HFO has been demonstrated using gas tracers and radioactive xenon. High frequency pendelluft has been suggested as a possible mechanism. We postulated that significant interregional mixing could occur without differences in regional time-constants, and tested this hypothesis in a four generation symmetrically branching system of rigid, 1 cm diameter tubes having a length/diameter ratio of 3.5. The model was filled with a 67% glycerol-water mixture and was oscillated in a fashion dynamically similar to the conditions existing within a tenth-generation human airway during HFO with a tidal volume of 75 ml and a frequency of 20 Hz. A 0.5 ml bolus of methylene blue was injected into a distal branch and was observed to spread laterally to all other airways within the system by convective streaming within 40 cycles. Diffusive mixing is negligible in this model. We conclude that convective streaming is a mechanism for lateral transport which allows significant interregional mixing in the absence of regional differences in time-constants. (Supported by NIH grant 5T32 HL07212.)

27.2

ENHANCED IN VITRO AIRWAY RESPONSIVENESS FOLLOWING REPEATED IN VIVO ANTIGEN CHALLENGE. E.M. Wagner,* S.R. Kleeberger,* E.Wm Spannhake, G.K. Adams. The Johns Hopkins Medical Institutions, Baltimore, Maryland 21205

We studied the effect of repeated antigen (Ascaris suum) challenge on airway reactivity in sheep. Fourteen sheep unselected as to skin test sensitivity to Ascaris were assigned to groups to be challenged with aerosolized saline or Ascaris. Airway reactivity was assessed in vivo with aerosolized histamine (10-300ug), PGF2α (10-300ug) and a stable analog of TXA_2 (1-30ug) on central airways (resistance) and more peripheral airways (dynamic compliance). The potency order was analog > histamine > PGF2α for both resistance and compliance. Following 5 bi-weekly challenges with Ascaris or saline aerosol, in vivo responsiveness to the test agents was unchanged in either group. In vitro responsiveness of trachealis and lung parenchymal strips from these two groups was also compared. Dose-response relationships were determined for each of the above agonists and methacholine over the range 10^{-8}M through 10^{-5}M. No difference in contractile response of trachealis was observed between the two groups. The order of trachealis response to 10^{-5} M of each agent was methacholine > histamine > PGF2α = analog. The order of responsiveness of parenchymal strips was analog > histamine > methacholine > PGF2α . Significant increases in responsiveness after antigen challenge were seen at the highest doses of analog (31% greater than saline control) and histamine (25% greater than saline control), whereas the responses to methacholine and PGF2α were unchanged. These data suggest that repeated antigen challenge in vivo may selectively increase the responsiveness of peripheral lung smooth muscle to certain chemical mediators of anaphylaxis.

27.3

TRACHEAL LUNG SOUNDS VERSUS END-EXPIRATORY PRESSURE IN EXCISED RAT LUNGS. L.D. Smith*, L.R. Brancazio*, N.E. Nehrig*, and D.G. Frazer, NIOSH, Dept. of Physiol. W.V.U., Morgantown, W.V. 26505

Excised rat lungs were inverted and placed in a saline filled plethysmograph housed in an anechoic chamber. The trachea was connected to a cannula which extended through the base of the plethysmograph, and the cannula was accoustically coupled to a pressure microphone used at grazing incidence. The lungs were inflated-deflated at a constant rate of change of transpulmonary pressure (30 cmH_2O/2min) by raising-lowering a fluid reservoir attached to the plethysmograph. A 6 cycle pressure-volume curve was recorded for each lung as the lung was inflated to TLC (30 cm H_2O) then deflated to progressively lower end-expiratory pressures of +6, +4, +3, +2, 0, and -5 cm H_2O for each of the 6 cycles. Tracheal lung sounds were not detected during lung deflation, and it was found that during lung inflation the index of lung sound, L (L=10 log $\int_0^1 [P(t)/Po]^2 dt$), was negligible when end-expiratory pressures were above 4 cm H_2O. L increased rapidly, however, between end-expiratory pressures of +4 and 0 cm H_2O. Only a small increase in L occurred between 0 and -5 cm H_2O end-expiratory pressures. These results are similar to those found previously for the relationship between trapped gas and end expiratory pressure. (Respir. Physiol. 36:121-129, 1979)

27.4

COMPARISON OF RADIOGRAPHIC AND FLUID MECHANICAL STUDIES OF NONHOMOGENEOUS SUBLOBAR LUNG SEGMENT INFLATION. L.E. Olson Ohio State University, Dept. of Veterinary Physiology and Pharmacology, Columbus, Ohio 43210.

A double lumen catheter was wedged in a subsegmental bronchus of excised caudal dog lung lobes (n=5). At fixed airway opening pressures (Pao=5,10,15 cm H_2O) pressure at the catheter tip (Ps) was increased in increments of 0.25 cm H_2O (0.25-2.0 cm H_2O) by increasing gas flow through the outer lumen of the catheter. Gas entered the distal lung segment and left through collateral channels. At fixed driving pressures (Ps-Pao) flow was altered by using He, Ne, N_2 or SF_6 as the inflow gas. Analysis of log-log plots of normalized pressure vs. Reynolds number (Moody plot) confirmed previous studies, suggesting that intrasegmental airway dimensions increased as Pao increased but were unaffected by increased Ps at a fixed Pao. Additional lobes were dusted with tantalum, a double lumen catheter inserted and radiographs taken at various airway opening pressures (Pao=0,5,8,10,25 cm H_2O) and driving pressures (0-25 cm H_2O) (n=3). Increasing Pao increased the diameter of intrasegmental and extrasegmental airways. At fixed Pao, increasing Ps decreased extrasegmental airway diameters but had a small and variable effect on intrasegmental airway diameters confirming the conclusions from the fluid mechanical analysis. The wedged catheter technique appears to measure the pressure-flow relationships of structures which behave like intrasegmental airways. (Minnesota Lung Assoc. & BSRG RR05465-21.)

27.5

NEURAL REGULATION OF BRONCHOMOTOR TONE IN THE INTACT MONKEY. R.J. Altiere*, J.L. Szarek* and L. Diamond. University of Kentucky, College of Pharmacy, Division of Pharmacology and Toxicology, Lexington, KY 40536.

Electrical field stimulation studies on airways isolated from the nonhuman primate lung have revealed a pattern of innervation similar to that found in humans, with a cholinergic excitatory and a nonadrenergic inhibitory pathway but no demonstrable adrenergic pathway. The present experiments were undertaken to determine if the nonadrenergic inhibitory system could be demonstrated in the nonhuman primate lung under in vivo conditions. Changes in lung resistance (R_L) were measured in five anesthetized, mechanically ventilated rhesus monkeys. To provide a background of enhanced airway smooth muscle tone, histamine was infused at a rate sufficient to increase R_L approximately 100 percent. Blockade of H_2 receptors with cimetidine (20 mg/kg i.v.) resulted in an additional increase in R_L. Under these conditions, electrical stimulation of the right cervical vagus nerve evoked a biphasic change in R_L (an increase followed by a decrease). The bronchoconstrictive phase of the response was blocked by atropine (1 mg/kg i.v.). The remaining relaxation phase persisted after beta adrenergic blockade with propranolol in a dose (1 mg/kg i.v.) that was sufficient to inhibit the decrease in R_L produced by epinephrine (5-10 µg/kg i.v.). These results are consistent with in vitro observations that neural inhibitory control of primate airways is nonadrenergic. Supported by Grant HL27025 from NHLBI.

27.6

PULMONARY EFFECTS OF ACUTE VANADIUM PENTOXIDE INHALATION IN MONKEYS. E.A. Knecht*, W.J. Moorman*, J.C. Clark*, D.W. Lynch*, and T.R. Lewis*. (SPON: F.N. Dukes-Dobos). DBBS, NIOSH, Cincinnati, OH 45226.

Pulmonary effects of acute vanadium pentoxide (V_2O_5) inhalation were studied in 16 cynomolgus monkeys. Two methods of inhalation exposure were used to facilitate detection of immediate and delayed reactions. An immediate reaction was studied by intrabronchial aerosolization of an aqueous solution of V_2O_5 (0.76M vanadium) while a delayed reaction was studied by evaluating responses on the day following a 6 hr dust aerosol exposure (5.0 mg V_2O_5/m^3). Results demonstrated both immediate and delayed reactions, with patterns of impairment indicative of central and peripheral airway obstruction. Since an immediate reaction occurred following inhalation of an aqueous aerosol, the time delay in reactivity to dust inhalation may be related to V_2O_5's poor solubility (0.07 g/l H_2O) and thus its bioavailability. Bronchoalveolar lavage was performed following V_2O_5 dust inhalation and demonstrated an increase in polymorphonuclear leukocytes, suggesting that the pulmonary function changes are due to chemically induced inflammation of the respiratory mucosa. Pre-exposure bronchial reactivity to methacholine did not correlate signiticantly with bronchial reactivity to V_2O_5 aerosols, indicating that pre-exposure bronchial reactivity to methacholine cannot be used to predict individual pulmonary reactivity to inhaled vanadium pentoxide.

27.7

CONTRACTILE PROPERTIES AND FATIGUE OF CANINE PARASTERNAL (PS) INTERCOSTAL MUSCLES. G.A. Farkas*, M. Decramer*, S. Cartwright*, D.F. Rochester and A. deTroyer. Meakins-Christie Lab McGill University, Montreal and Pulmonary Division, University of Virginia, Charlottesville, VA 22908.

The PS are employed at all levels of breathing, and their contractile characteristics could influence their role as inspiratory synergists to the diaphragm (DPM). To assess the relationship between the PS and the DPM, we characterized their in-vitro isometric contractile properties. We also related sonometrically measured PS length at FRC (L_r) to in-vitro optimal force generating length (L_o). Maximal tetanic force (Po, Kg/cm^2) was 2.2 $\pm$ SEM 0.2 for PS and 1.7 $\pm$ 0.1 for DPM (P<.05). PS twitch speed was faster than DPM (P<.01), thus displacing the relative PS force-frequency curve to the right of the DPM curve. However, absolute PS force was 0.7 DPM force at 20 Hz (P<.05) and 1.0 DPM force at 35 Hz. The ascending limb of the PS tetanic length-tension curve lay below the DPM curve; at 85% L_o, PS force was 46% Po whereas DPM force was 87% Po (P<.01). PS in vitro length was 91% of L_r (P<.01). In vitro fatigability of PS and DPM were similar. We conclude that under in vivo conditions, PS produces less absolute force than DPM, owing to differences in twitch and length-tension characteristics. Since PS length at FRC exceeds L_o, increasing lung volume tends to increase PS force more than DPM force. Thus, PS and DPM synergism appears to maintain available inspiratory pressure over a wide range of lung volumes. (Supported by P.B. Francis Found. & HL 21500).

27.8

CONTRACTILE PROPERTIES AND FATIGUE OF CANINE NECK ACCESSORY AND ABDOMINAL RESPIRATORY MUSCLES. D.F. Rochester, M.Decramer*, S. Cartwright*, A. deTroyer and G.A. Farkas*. Pulmonary Division, University of Virginia, Charlottesville, VA 22908.

During high respiratory loads, both neck accessory inspiratory and abdominal expiratory muscles are recruited. To assess the influence of these muscles on the chest wall, we studied mechanical characteristics of rectus abdominus (RA), external oblique (EO), sternomastoid (Sm) and scalene (Sc) muscles. Isometric contractile properties were evaluated in an in-vitro bath at 37°C. There were no differences among these 4 muscles with regard to twitch speed, maximum tetanic tension or length-tension characteristics. The force-frequency curves of EO and Sc were shifted to the right of RA and Sm curves, e.g. at 20 Hz and 35 Hz, EO and Sc produced about 15% and 10% less force than RA and Sm, respectively (P<.05). Fatigue was assessed by repeatedly stimulating the muscles with 60 trains per minute (duty cycle, 0.35) at a frequency of 35 Hz. Following 50 sec of repeated stimuli, force in EO and Sc fell 25% while in RA and Sm it fell 55% (P<.01). This may only reflect their positions on the force-frequency curve. Relative to the diaphragm, RA, EO, Sm and Sc are faster, but have virtually identical length tension curves. These characteristics would be appropriate for muscles subserving both respiratory and non-respiratory functions, but at present the in vivo operating lengths of these muscles are not known. (Supported by the Parker B. Francis Foundation and HL 21500).

27.9

EFFECTS OF VELOCITY OF SHORTENING OF RESPIRATORY MUSCLE ENDURANCE. D. McCool*, D. McCann*, D. Leith and F.G. Hoppin, Jr. Memorial Hospital, Pawtucket, RI 02860, Brigham and Women's Hospital, Boston, MA 02115

In a study of respiratory muscle fatigue, Bellemare and Grassino (JAP 53, 1190) found that endurance of the diaphragm was a function of a Pressure Time Index (PTI) i.e. the product of fractional pressure load (Pdi/Pdi max) and duty cycle (T_I/T_{TOT}). We postulated that shortening velocity would have an independent effect on endurance. We studied 4 subjects, breathing to exhaustion, with varied inspiratory resistors and target PTIs (measured in the esophagus and displayed on-line). VT, T_I/T_{TOT}, PCO_2, and chest wall configuration were constant. Endurance time (T_{LIM}) was the point when the target PTI could no longer be maintained. For each resistor, endurance (T_{LIM}) increased as the load (PTI) decreased but lower resistance (higher flows and therefore higher velocities at the same PTI) substantially decreased the T_{LIM} (Fig.1). For constant T_{LIM}, the load decreased linearly with velocity (Fig.2). We conclude that velocity of shortening of the respiratory muscles is an important and independent determinant of their endurance.

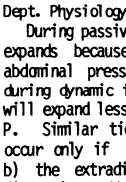
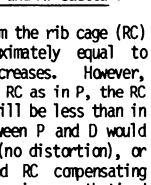


Fig. 1 (left) one subject, resistor orifices from 2.5 mm (□) to unloaded (o). Fig. 2 (right) same experiments, for T_{LIM}s 8 m (o) and 1m (*).



27.10

DETERMINATION OF THE STERNOCLEIDOMASTOID MUSCLE FUNCTION USING HEAD LIFT. D. Renald Lemieux*, Donald B. MacHattie*, and L. David Pengelly. Dept. of Engineering Physics, Electrical Eng., and Medicine, McMaster University, Hamilton, Ontario, Canada, L8S 4L8.

We contrasted two functions of the Sternocleidomastoid (SCM) muscle: forward flexion of the neck and inspiratory motion of the chest wall. Four normal males, in the supine position, were studied. We recorded mass lifted with the head or head lift (HL) and inspiratory muscle pressure (Pmusc) in addition to Sternocleidomastoid EMG (EMG_{SCM}). Graded efforts of HL and Pmusc were executed, under static conditions, at two head heights above the bed, 3cm and 10cm, and at five different lung volumes above FRC. HL was measured with a self-contained transducer system located under the subject's head. Values of Pmusc were obtained from pressure transducer records by adding the pressure-volume relaxation curve to the inspiratory mouth pressure-volume curve.

From the normalized data: 1) The Force (HL or Pmusc)-EMG relationship was found to be linear ($r^2 > 0.95$); 2) Lung volume did not change significantly the above relationship ($p < 0.05$). Data for all subjects at all lung volumes were pooled to form a more generalized Force-EMG relationship; 3) Using the EMG_{SCM} as the common factor, a relationship between Pmusc and HL was found for both head heights (Pmusc = f(HL)). At 10cm of head height, Pmusc = 0.494 + 0.386 HL, while at 3cm, Pmusc = 0.494 + 0.112 HL. (Supported by: Hamilton Civic Hosp. Foundation; Hamilton and Ontario Lung Associations.)

27.11

MECHANICAL ASPECTS OF RIB CAGE DISTORTION. J.P. Mortola and M. Saetta*. Dept. Physiology, McGill University, Montreal, Canada.

During passive inflation (P) of the respiratory system the rib cage (RC) expands because the pressure applied to it (approximately equal to abdominal pressure Pabd, Goldman and Mead, 1973) increases. However, during dynamic inspiration (D) if Pabd is not acting on RC as in P, the RC will expand less, hence lung volume, for a given Pabd, will be less than in P. Similar tidal volume (Vt)-Pabd relationships between P and D would occur only if a) Pabd acts on RC equally in P and D (no distortion), or b) the extradiaphragmatic inspiratory muscles expand RC compensating distortion. We measured Vt, Pabd, RC and ABD movements in anaesthetized adult rats, and Vt, RC and ABD in sleeping human infants, two species with high chest wall/lung compliance ratios. The end inspiratory point of the Vt-Pabd (or Vt-ABD) relationship was compared with the passive curve, obtained by occluding the airways during expiration. For a given Pabd (or ABD) in D Vt averaged 50% (rats) and 49% (infants) of that in P. With stimulation of the phrenic nerves in rats Vt was only slightly less than in D, indicating that in D the system was essentially driven only by the diaphragm. In both species occasional breaths with large RC expansion occurred, and the D points fell then on the P curve. In rats and infants the effective compliance (Vt/peak airway pressure during an inspiratory effort) was 54% and 60% respectively of the passive compliance. We conclude that in infants 1) the volumetric RC distortion decreases Vt to less than 50% of the passive value, 2) RC distortion is probably the major contributor to the difference between active and passive compliance, and 3) being on the 'relaxation' curve reflects compensated distortion and not absence of it.

27.12

CHANGES OF LUNG COMPLIANCE, AIRWAY RESISTANCE AND BREATHING EFFECTIVENESS IN EXERCISING DOGS. A.R. Jayaweera,* H.J. Quebbman* and W. Ehrlich. The Johns Hopkins Univ., Sch. of Hygiene, Baltimore. MD. 21205

The respiratory functions of 6 dogs during treadmill excercise (1.5mph. 9° inclination) were compared with rest values. The cardiac output increased by 70% and elevated pulmonary artery pressure by 8 mmHg. Inspiratory V(min) increased from 14.3 + .7 to 27.6 + 2.3 L/min. Resp.f, insp. V(peak), T(i)/T(t) were significantly increased. V_m decreased from 511 + 24 to 455 + 17 ml. Pleural pressure time index (PPTI) increased from 1.25 + .15 to 2.70 + .33 mm Hg. Lung compliance did not change significantly (121.2 + 7.7 (rest), 117.4 + 19.1 (excercise) ml/mm Hg). Airway resistance remained unchanged (.0391 + .0034 (rest), .0388 + .0043 (excercise) mm Hg/ (L/min)). Breathing effectiveness index (insp. V(min)/PPTI) also remained unchanged (13.4 + 1 (rest), 13.6 + 1.5 (excercise) L/(min. mm Hg)). The effect of the changes in pulmonary circulation was insufficient to decrease the lung compliance significantly. We hypothesize that the increased respiratory airflow enhanced the turbulance in the airway and this increased the airway resistance. However this increase could have been nullified by the effect of enhanced beta adrenergic activity on the smooth muscles in the airway.

(Supported by USAMRDC contract DAMD 17-83-C-3182)

27.13

REGIONAL COMPARISON OF HISTOCHEMICAL PROPERTIES IN THE DEVELOPING BABOON DIAPHRAGM. J.F. Villanacci*, L.C. Maxwell and T.J. Kuehl*, Depts. of Physiology, Univ. of Texas Health Science Center and the Southwest Foundation for Research and Education, San Antonio, TX 78284

We tested the hypothesis that regional differences in development within baboon diaphragm muscles would exist. Fibers in substernal, crural, and costal regions of the diaphragm in premature (139 days gestation), newborn (full term), and adult (5 - 18 yrs.) animals were classified as Type I, IIA, IIB and IIC based upon standard criteria. We also describe a developing fiber (termed IIH) which had a halo appearance in the NADH-TR reaction. In premature animals the substernal region had a greater proportion of IIC and a lesser proportion of IIA fibers than other sites. There were no regional differences in mean fiber area (MFA) in the premature diaphragm nor in MFA or composition in newborn or adult diaphragm. There were no sex differences in composition at any age, however, MFA was significantly greater in adult males compared to females. Fibers grew from a MFA of 171 ± 19 μm^2 in premature animals to 2830 ± 180 and 4005 ± 234 μm^2 in adult female and male animals respectively. The proportion of fiber types changed from 16.5 ± 3, 20.7 ± 2, 7.2 ± 3, 0 and 55.7 ± 2 percent in the premature animals (Types I, IIA, IIH, IIB, and IIC respectively) to 45.0 ± 2, 18.5 ± 1, 0, 36.1 ± 2 and 0.5 ± 2 percent in the adults.
(Supported by NIH grant HL29977).

NEURAL CONTROL OF CIRCULATION

28.1

DIRECT VERSUS INDIRECT CHOLINERGIC EFFECTS ON CARDIAC CONTRACTION AND CONDUCTION. D.V. Priola, T. Blomquist and C. Anagnostelis. Univ. of New Mexico, Albuquerque, N.M. 87131

There is some question whether the negative inotropic effects of acetylcholine (ACh) and vagal stimulation on ventricular muscle are direct or require ongoing adrenergic activity to be effective. Recent in vitro data suggest that the latter is dominant, with negligible direct actions. However, in vivo or in situ data have suggested that direct cholinergic inhibition is an important mechanism. We have explored these possibilities in the canine heart in situ. ACh injections (0.5-5.0 mcg) were given intracoronary to 15 dogs on cardiopulmonary bypass while right ventricular isovolumic pressure (RVP) and His bundle activity (His) were measured. Negative cholinergic responses were evaluated during control, isoproteronol infusion (IS), stellate ganglion stimulation (SS) and after beta adrenergic blockade (BB). Effects of ACh on RVP were enhanced during both IS (+75%) and SS (+175%). No enhancement of dromotropic effects was observed. Following BB, direct effects of ACh on both conduction (+12%) and contractility (-15%) were still prominent. Our data show that both direct and indirect actions of ACh contribute to the negative inotropic and dromotropic effects of vagal stimulation. The degree depends upon whether inotropic or dromotropic changes are involved and whether the competition is with circulating catecholamines or with sympathetic neural activity.
(Supported by Grant No. HL-18517 from the NHLBI).

28.2

EFFECT OF EPINEPHRINE AND NITROPRUSSIDE ON CAROTID SINUS DIAMETER, COMPLIANCE, AND PRESSURE IN THE DOG. Leonard B. Bell and John P. Karpine. Depts. Anes. & Physiol. Med. Col. of Wisconsin and VA Medical Center, Milwaukee, WI 53193.

Epinephrine decreases and nitroprusside increases carotid sinus diameter (CSD) when perfused through the isolated carotid sinus. This study was designed to determine the effect of epinephrine and nitroprusside on carotid sinus pressure (CSP), compliance (CSC) and CSD simultaneously in an isolated, constant flow-perfused carotid sinus. The left carotid sinus was vascularly isolated in dogs, anesthetized with NA pentobarbital (35 mg/kg). The common and external carotid arteries were cannulated and perfused with heparinized, oxygenated, lactated Ringers solution (1200 ml) using a device to measure CSP and CSC continuously as previously described (Physiol. 26(4):102, 1983). Similar perfusates containing epinephrine (1 mg) or nitroprusside (50 mg) were used after control values were determined. CSD was measured using sonomicrometer length gauges attached to the medial side of the sinus and lateral side of the common carotid. Control values of CSP, CSD, and CSC were 93.6±2.9 mmHg, 8.581±0.683 mm and 2.155±0.297 µl/mmHg, respectively. The addition of either epinephrine or nitroprusside to the perfusate did not significantly alter CSP or CSC. However, CSD decreased and increased significantly with epinephrine and nitroprusside perfusates, respectively. This study demonstrates that vasoactive agents can change CSD independently of CSC and CSP. (Supported by NIH GM 29641 and the VA).

28.3

INFLUENCE OF NIFEDIPINE LEVELS ON RABBIT CAROTID BARORECEPTOR NERVE ACTIVITY. H. Stinnett and C. Roller*. UNDSM, Grand Forks, ND 58202.

Excitatory effects of nifedipine (NF) on carotid sinus (CS) baroreceptor nerve activity (BNA) are dependent on Ca^{2+} mechanisms (Heesch, et. al., AJP 245: H653-H661, 1983). Because NF is a slow Ca^{2+} channel inhibitor, with no known influence on neuronal Ca^{2+} channels, we suggest it would target CS smooth muscle, rather than nerve. In rabbit CS, smooth muscle is located in tunica media and adventitia, while, baroreceptors are not found in media. We hypothesized the relationship of BNA to intrasinus pressure (ISP) would vary dependent on NF inhibition of smooth muscle in media and then media and adventitia. In six anesthetized rabbits the right CS was vascularly isolated and perfused with Ringer's solution and then Ringer's plus NF (range 1×10^{-8} to 5×10^{-6}M). Access of NF to tissue layers was limited to diffusion process. At each 1 min. nonpulsatile ISP step of 25 mm Hg (range 25-125 mm Hg) BNA was recorded for the last 15 sec. BNA was then integrated and normalized (Ringers control BNA = 100% at ISP = 100 mm Hg) for comparisons. With respect to controls, NF at an average of 3.3×10^{-7} M elevated % BNA over the ISP range; yet NF at 1.3×10^{-6} M depressed % BNA over the ISP range. Results are consistant with a model in which baroreceptors function in parallel with media and in series with adventitia smooth muscle. Support in part BRS #SO7-RR05-407-22; N.D. Med. Ed. and Rs. Foundation; AHA, Dakota Aff. #510.

28.4

BIMODAL EFFECTS OF NOREPINEPHRINE ON RAT AORTIC BARORECEPTORS IN VITRO. P.A.Munch and A.M.Brown, Univ. of Texas Medical Branch, Galveston, Texas 77550.

The effects of norepinephrine (NE) on single baroreceptor (BR) units were studied using an in vitro aortic arch-aortic nerve preparation. Aortic diameter and BR discharge were recorded simultaneously while perfusing at a constant surpathreshold pressure. When discharge was stable NE was added to the perfusate in cumulative doses. "Low" doses (10^{-10}-10^{-7}M) reduced discharge in a dose-dependent manner concomitant with vasoconstriction. The reduction in discharge was attributed to "unloading" of the BRs. Similar results were obtained with angiotensin II (AII). By contrast, "high" doses of NE (10^{-6}-10^{-5}M) increased discharge dramatically despite the decrease in diameter; excitation was not observed with AII. The smooth muscle relaxant sodium nitroprusside (10^{-6}M) prevented NE-evoked vasoconstriction and BR unloading, but not BR excitation. With the $alpha_1$ adrenergic antagonist prazosin (10^{-6}M) aortic vasoconstriction and BR unloading occurred at higher doses and BR excitation did not occur. The beta blocker propranolol (10^{-6}M) had no effect. These results indicate NE has two dose-dependent modes of action on aortic BRs: (1) mechanical unloading of the neural endings due to smooth muscle contraction, and (2) direct excitation. Both smooth muscle and BR excitation may be mediated by $alpha_1$ adrenoceptors. The net change in BR discharge at constant pressure will depend on which of these effects predominates. (This work supported by HL-16657 and GM-07856)

28.5

CARDIOVASCULAR REFLEXES EVOKED BY C-FIBER BARORECEPTORS IN THE CAROTID SINUS OF DOGS. H.D. Schultz, T.E. Pisarri*, H.M. Coleridge, and J.C.G. Coleridge. Cardiovascular Research Institute, University of California San Francisco, San Francisco, CA 94143.

Carotid sinus baroreceptors are supplied by myelinated A-fibers or by non-myelinated C-fibers. We have attempted to determine whether selective stimulation of the C-fiber baroreceptors evokes reflex changes in hindlimb vascular resistance and heart rate. In chloralose-anesthetized dogs, we perfused the carotid sinuses with a pulsatile pressure (mean 100 mm Hg). We perfused the hindlimbs with blood at constant flow. The influence of input from other baroreceptor areas was eliminated by cutting the vagus nerves. Increasing carotid sinus pressure by 60-80 mm Hg decreased hindlimb vascular resistance 51% and heart rate 24%. After A-fiber baroreceptors had been selectively blocked by cooling the sinus nerves to 7°C, a similar increase in carotid sinus pressure decreased hindlimb vascular resistance 23% and heart rate 8%. All responses to carotid sinus distension were abolished by cooling the nerves to 0°C. Our results indicate that C-fiber baroreceptors in the carotid sinus can reflexly decrease sympathetic outflow to the heart and hindlimb vascular bed.

(Supported by HL-25847 and HL-07192.)

28.6

EFFECTS OF LEFT VENTRICULAR RECEPTOR STIMULATION ON REGIONAL VENOUS RESISTANCE. S.C. Walgenbach, J.L. Seagard, M. Duvall*, and J.P. Kampine. Depts. Anes. & Physiol., Med. Col. of Wisconsin and VA Medical Center, Milwaukee, WI 53193.

Few studies have examined the role of left ventricular (LV) receptors in the regulation of venous tone. This study in chloralose-anesthetized dogs examined the effects of stimulation of LV receptors, through occlusion of the left anterior descending artery (LAD), on reflex resistance in two venous beds: 1) saphenous and 2) mesenteric veins. Previous studies have shown that the mesenteric venous resistance decreases in response to elevations of carotid sinus pressure (CSP). To verify reflex responsiveness of the mesenteric bed and to examine the interaction of carotid sinus (CS) baroreceptors and LV receptors on venous resistance, the CS was vascularly isolated and perfused at low (50), medium (120), and high (190mmHg) pressures during LAD occlusion. Venous resistances were determined by measuring changes in perfusion pressure during constant flow perfusion of the 1) lateral saphenous and 2) mesenteric veins. Saphenous venous resistance did not change in response to changes in CSP or LAD occlusion. Mesenteric resistance reflexly decreased and increased in response to appropriate changes in CSP. Mesenteric resistance reflexly decreased in response to LAD occlusion at low and medium CSP by approximately 10%. Thus, mesenteric, but not saphenous, venous resistance appears to be under reflex regulation of the CS baroreceptors and LV receptors. (Supt. by NIH GM 29641, Wis. Heart #83-GA-33, and the VA).

28.7

CARDIAC SYMPATHETIC AND PARASYMPATHETIC EFFERENT ACTIVITIES DURING ACUTE BLOOD PRESSURE CHANGES IN THE PUPPY. Gilbert R. Hageman, Brett H. Neely, L. Richard Smith* and Ferdinand Urthaler. Univ. of Alabama in B'ham, Birmingham, AL 35294.

In 7 anesthetized puppies (6-10 wks, 1-6 kg) heart rate (HR) and blood pressure (BP) were recorded before and during acute BP changes achieved with nitroglycerin (NTG) and phenylephrine (PEP) (2 to 8 μg/kg I.V.). After control responses, one sympathetic (right stellate cardiac) and one parasympathetic (right vagus) cardiac nerve were identified and multifiber efferent nerve activity recorded and analyzed by microprocessor. BP responses to drugs were not significantly affected by nerve sectioning (before and after: NTG decreased BP by 29±5% vs 27±4%; PEP increased BP by 34±4% vs 27±7%). In contrast HR responses were significantly attenuated (before and after: NTG increased HR by 18±9% vs 3±5%; PEP decreased HR by 15±11% vs 3±2%). Sympathetic nerve activity correlated with BP changes increasing to 116± 5% of control with NTG and decreasing to 82±10% of control with PEP. The same was true for parasympathetic activity which increased to 110±10% of control with PEP and decreased to 87±12% of control with NTG. Thus severing these 2 cardiac nerves for recording purposes attenuates the HR responses to BP changes. However, the recording of nerve activity which closely parallels BP changes can be used to assess regional influence of baroreceptor regulation. (Supported by NIH grants HL 17,667 and HL 31,536).

28.8

EFFECTS OF ISCHEMIA AND HYPOXIA ON ABDOMINAL VISCERAL AFFERENTS IN CATS. John C. Longhurst and Lisa E. Dittman*. University of California, San Diego, La Jolla, CA 92093

Ischemia of abdominal visceral organs reflexly affects the cardiovascular system. However, the types of afferents and mechanisms of stimulation during ischemia are not known. Thus, in 11 anesthetized cats we recorded impulse activity of afferents in the right splanchnic nerve during ischemia or systemic hypoxia (thoracic aorta occlusion or $\downarrow F_{IO_2}$). We also examined the afferent responses to bradykinin (BK)(10μg, ia) and prostacyclin (PGI_2)(1-10μg, ia). Five of 12 C fibers (cv=1.0±.39 m/sec mean±SD) and 5 of 15 A fibers (cv=20±18 m/sec) were stimulated by ischemia and/or hypoxia. Each afferent innervated one receptive field in the pylorus, intestine, porta hepatis or pancreas. Activity of C fibers increased from 0.3±0.3 to 1.6±1.4 imp/sec after 90±38 sec, while A fiber activity increased from 0.2±0.4 to 4.4±6.9 imp/sec after 50±43 sec. Four of the 5 A fibers were slowly adapting. Three C and 2 A fiber endings responded only after sensitization with BK and PGI_2. Also, BK stimulated 4 A and 4 C fiber endings and PGI_2 3 C and 2 A fiber endings. Hypoxia stimulated the endings after 62±22 sec at PaO_2's of 52 to 7 mmHg (normal pH and $PaCO_2$), well after the increase in blood pressure at 43±27 sec. Thus, although ischemia and hypoxia stimulate many A and C endings, these receptors are not sensitive to mild hypoxia like carotid and aortic body chemoreceptors. These endings also may respond to ischemia-induced local release of BK or PGI_2. (AHA 83-758 and NIH NS 20165)

28.9

SPECIFIC PRESSOR ACTIONS OF ANGIOTENSIN II IN THE NUCLEUS TRACTUS SOLITARIUS OF SPONTANEOUSLY HYPERTENSIVE RATS. Rod Casto and M. Ian Phillips. Dept. of Physiology. Univ. of Florida. Gainesville, Fla. 32610.

Microinjection of Angiotensin II (ANG II) into the nucleus tractus solitarius (NTS) of urethan-anesthetized rats produces a dose-dependent rise in arterial pressure. Pretest injections of 100ng ANG II in normotensive rats produced a rise in mean arterial pressure of 9.4 ± 0.8 mmHg. Using double-barrel micropipettes to inject 100nl volumes, we found that injection of the ANG II antagonist, saralasin (1ug) into the NTS two minutes before injection of ANG II (100ng) abolishes the pressor response. Thirty minutes after saralasin treatment, 100ng of ANG II microinjected into the NTS produced a pressor response of 7.4 ± 1.0 mmHg, indicating that the blockade of angiotensin receptors was reversible. In a comparison of normotensive versus spontaneously hypertensive rats (SHR), the pressor response over a dose range of 50-500ng ANG II was significantly larger in SHR. This study suggests that central ANG II specifically activates the NTS producing an increase in blood pressure, and that the responsiveness in this model of hypertension is increased. (This work supported by NSF and NIH grants.)

28.10

EVIDENCE THAT THE PRESSOR REGION OF THE FASTIGIAL NUCLEUS (FN) CAN ALSO AFFECT RESPIRATION AND MAY ACT TO INTEGRATE RESPONSES OF THE CARDIOVASCULAR AND RESPIRATORY SYSTEMS. L. O. Lutherer and J. L. Williams*. Departments of Physiology and Internal Med., Texas Tech Univ. HSC, Lubbock, TX 79430

Moruzzi originally showed that stimulating cerebellar cortex altered respiration. We and others also observed respiratory changes while stimulating the pressor region of the FN. In this study, sites in and around the FN were stimulated in 5 cats anesthetized with chloralose - urethane. All 15 sites giving an increase in arterial pressure produced a concurrent change in respiration and were confirmed histologically to lie in the ventral medial portion of the rostral FN. The thresholds and response patterns as a function of stimulus frequency and intensity appeared equivalent for both responses. Both were stimulus locked at onset, but the respiratory showed an after-discharge lasting 1-4 min. Minute volume increased due to changes in frequency of breathing but not tidal volume. At low stimulation frequencies, all respiratory responses were excitatory. As stimulus frequency was increased, a transient apnea (up to 20 sec) followed by an increased rate before or just after removal of the 30-sec stimulus (6 sites, 2 cats) or gasping (3 sites, 1 cat) were occasionally observed. The close linkage between the respiratory and cardiovascular responses in this restricted region of the FN suggest that some level of integration between these two systems may reside within the FN. (Supported by AHA grant 82-1235 and Tarbox Institute TTUHSC).

28.11

CARDIAC ARRHYTHMIAS AND SUDDEN DEATH IN DOGS DURING CLASSICAL AVERSIVE CONDITIONING: THE ROLE OF SHOCK PREDICTABILITY. D.C. Randall, K.C. Claxon*, and R.A. Wilson*. Dept. Physiol. and Biophys., Univ. Kentucky, Lexington, KY 40536.

A reliable paradigm for evoking "stress induced" ventricular ectopic beats (VEB) or ventricular fibrillation (VF) in animals could be used to study the basis and prevention of sudden death in man. We tested 2 groups of dogs using discriminative classical aversive conditioning as an "emotional stress". Both groups received a 30 sec. tone (CS^+) followed by a 1/2 sec. shock and another 30 sec. tone (CS-) without shock. Group 1 (n=2) was fully trained in this discriminative task: Average heart rate (HR) increased from 64/min. during control to a peak of 115/min during CS^+, but did not change during CS-. The tone/shock pairing was then given at 3 min. into a 4 min. left circumflex (LCx) coronary artery occlusion (CAO). VEB did not increase during these CAO trials. VEB did increase in Group 2 (n=3). There was no prior discriminative conditioning training in these dogs. Instead, using the identical CAO protocol, the 5th CS^+/shock trial, and every 5th such trial thereafter was performed during a LCx CAO. Two of these dogs experienced VF during the occlusions, one on the 1st and one of the 5th. Neither sudden death dog had learned to discriminate, since HR increase an average of 52/min. during the CS-. These data indicate that classical aversive conditioning may be very arrhythmogenic when conducted during CAO if the subject is unable to predict the occurrence of shock. (HL 19343)

ENVIRONMENTAL/TEMPERATURE/EXERCISE

29.1

EFFECTS OF HIGH DOSE LOCALIZED COBALT-60 GAMMA RADIATION ON THE CANINE HEMATOPOIETIC SYSTEM. M.B. Cockerham*, T.J. MacVittie*, M.L. Patchen*, and L.M.K. Wathen*. (SPON: P.J. Gunter-Smith). Experimental Hematology Department, Armed Forces Radiobiology Research Institute, Bethesda, MD 20814

Determination of a valid human radiation response requires a large animal model of similar body dimensions, $LD_{50/30}$ and distribution of radiation dose with tissue depth. This report utilizes the canine exposed to acute midline tissue dose delivered bilaterally, to only the right quadrant of the chest. Four adult male beagle dogs were exposed bilaterally (dose rate of 40 rad/min) to 1200 rads midline tissue dose from the AFRRI cobalt-60 Theratron 80. Bone marrow was sampled from irradiated and nonirradiated (shielded) ribs following exposure. Granulocyte/macrophage progenitor (GM-CFC) cells were assayed at various intervals postexposure. GM-CFC were undetectable in the irradiated ribs until 2 days postexposure. Content rose slowly through day 12, followed by a sharp rise to normal values over the next 6 days. An overshoot followed through 27 days postexposure. The GM-CFC in the shielded ribs showed a decrease to values approximately 50% of control within 48 hr after exposure. These values recovered quickly to within normal levels and remained so with oscillations through the period of observation. The data indicate that surviving stem cells emigrate to irradiated marrow sites and proliferate. Seven days are required for seeding and amplification to detectable levels. Peripheral blood leukocyte and platelet levels are not correlated with the marrow damage.

29.2

BODY TEMPERATURE RESPONSES INDUCED BY BETA-ENDORPHIN IN RATS AT 24.5 C. A.R. Gwosdow* and E.L. Besch. Department of Physiological Sciences, College of Veterinary Medicine, University of Florida, Gainesville, FL 32610

The role of the adrenal and thyroid glands in mediating the body temperature responses caused by beta-endorphin (B-END) were examined in male, Sprague-Dawley rats in a controlled environment room at 24.5 ± 0.1C. Relative humidity of 50 ± 0.3% and a 12L:12D photoperiod (L=0900 to 2100 hr) were maintained. Rectal temperature (Tr) was measured using thermistors, corticosterone and thyroid hormones by radioimmunoassay. Intracerebroventricular (IVT) administration of varying doses (0.05 to 50 µg) of B-END resulted in a dose-related hyperthermia that began 30 min post-IVT injection and continued for 1 hr. Intravenous injections of these doses of B-END did not increase Tr. The B-END-induced hyperthermia was antagonized by naloxone. Pretreatment with propranolol, phentolamine or both drugs in combination did not block the hyperthermia caused by B-END. Adrenalectomized or hypophysectomized rats receiving IVT injections of B-END did not consistently display an increased Tr. Beta-endorphin administration had no detectable effect on serum corticosterone but appeared to inhibit serum triiodothyronine. These data suggest that the hyperthermic action of B-END is mediated centrally through opiate receptors and does not involve adrenergic receptors.

29.3

A MICROCOMPUTER CONTROLLED TEMPERATURE DATA ACQUISITION SYSTEM EMPLOYING RAPID, HIGH PRECISION CALIBRATION OF THERMISTORS OR PLATINUM RTD'S. William T. Matthew* and Patricia C. Szlyk. US Army Res. Inst. Environ. Med., Natick, MA 01760

A microcomputer controlled, high precision temperature data acquisition system for physiological applications is described. Hardware consists of a Hewlett-Packard model HP-85 computer, 3465A digital voltmeter, 3495A scanner/multiplexer, 2804A quartz thermometer (absolute accuracy ± 0.04°C) and a Braun model 1480-E constant temperature circulator with 6 L water bath (stability ± 0.004°C). The system permits the acquisition of up to 40 channels of temperature data from either thermistors or platinum resistance thermometer devices (RTD's) at rates of 2 channels/sec. An essential feature of the system is the incorporation of hardware/software components which provide rapid individual calibration of each temperature probe. Probe resistances and the quartz thermometer reading are determined at 3 bath temperatures spanning the desired temperature range. These measures are used to compute resistance to temperature conversion factors which are stored for subsequent use on-line. Precision of temperature measurements obtained using 10 calibrated probes was evaluated for 10 trials per probe by comparing quartz thermometer and individual probe readings at bath temperatures ranging from 26°C to 42°C (1°C increments) and was found to be ± 0.004°C with a worst case individual probe deviation from the quartz thermometer of 0.009°C. This system has enabled us to obtain very accurate on-line multiple site temperature measurements in both human and animal studies.

29.4

FURTHER CHARACTERIZATION OF AN ENDOGENOUS CRYOGEN THAT APPEARS IN URINE. D.G. Burt*, T.C. Holland*, S.M. Eiger*, M.J. Kluger. The Univ. of Mich. Med. School, Ann Arbor, MI 48109.

Urine contains a substance which when injected intravenously into laboratory rabbits causes a dose-dependent fall in rectal temperature along with peripheral vasodilation as demonstrated by an increase in earskin temperature. Previous work in our lab has shown this "endogenous cryogen" to be heat labile at 97°C, to have an apparent size of 40,000 daltons based on gel filtration, and to be insoluble in chloroform or ether. Isoelectric focusing of crude material indicates a pI of 2-4. This material, which appears to be a protein, was precipitated in 60-80% saturated ammonium sulfate and the pellet redissolved in warm saline. The cryogen was bound to a DEAE agarose ion exchanger from 50mM NaCl and was eluted with 150-200mM NaCl. Analysis of this fraction by SDS-PAGE revealed the presence of 7-8 protein bands. A cryogenic response consisting of a 0.2-0.3°C fall in rectal temperature and a 4-7°C rise in earskin temperature was produced after injecting either 10ml of unprocessed urine or 0.75ml of the active ion exchange fraction. The protein concentration of the urine was 200ug/ml and that of the ion exchange fraction was 30-40ug/ml. In terms of activity per ug. of protein this represents 100-fold purification. (Supported by.Mich. Kid. Found. and NIH 5T32RR07008-07).

29.5

INFLUENCE OF HEAT STRESS AND ACCLIMATION ON MAXIMAL AEROBIC POWER. Bruce S. Cadarette*, Andrew J. Young, Leslie Levine*, Kent B. Pandolf and Michael N. Sawka. US Army Research Institute of Environmental Medicine, Natick, MA 01760

Thirteen healthy male volunteers (age, 22 yr; ht, 176 cm; wt, 76 kg; surface area, 1.92 m^2) performed discontinuous cycle ergometer maximal oxygen uptake ($\dot{V}O_2$ max) tests in temperate (21°C, 30% rh) and hot (49°C, 20% rh) environments, before and after a nine-day heat acclimation program involving two hours of treadmill walking at 45% of $\dot{V}O_2$ max. This program resulted in significantly decreased ($p < 0.01$) final heart rate (24 b $\cdot$ min^{-1}) and rectal temperature (0.4°C) from the first to last day of acclimation. The $\dot{V}O_2$ max decreased ($p < 0.01$) in the hot environment relative to the temperate both before (-8%) and after (-7%) acclimation with no significant difference ($p > 0.05$) shown for power output (PO, watts) between environments either before or after acclimation. The $\dot{V}O_2$ max was higher ($p < 0.01$) after acclimation in both the temperate (3%) and hot (4%) environments. PO also was higher ($p < 0.05$) after acclimation in the temperate (4%) and hot (2%) environments. The reduction in $\dot{V}O_2$ max in the hot compared to temperate environment was not significantly correlated ($p > 0.05$) with the difference in core temperature at $\dot{V}O_2$ max between temperate and hot trials ($r = 0.36$), nor was it significantly correlated with aerobic fitness level ($r = -0.29$). These findings indicate that heat stress, per se, reduced the $\dot{V}O_2$ max. Further, the reduction in $\dot{V}O_2$ max due to heat was not affected by state of acclimation, the degree of elevation in core temperature, or level of aerobic fitness.

29.6

QUANTITATING THE CHOLINERGIC DOSE-RESPONSE CHARACTERISTICS OF HUMAN ECCRINE GLANDS BY IONTOPHORESIS. Kenneth K. Kraning, Paul A. Lehman, and Roger G. Gano. Univ. of Washington, Seattle, WA 98195.

Iontophoresis (IP) is a non-invasive procedure for rapidly transporting ionic drug molecules across the skin barrier. In studying sweat gland function IP has often been used to stimulate or block but never to generate graded dose-response (D-R) data. We have found it possible to use IP in a more quantitative fashion with acetyl-β-methacholine HCl (MCh), obtaining relative D-R data on eccrine glands by varying the current (i), the duration (t), and the ratio of active:inert ions in a fixed molarity treatment solution. Four to eight 2.1 cm D skin sites on the volar forearm surfaces of normal subjects were preconditioned by IP with 20 mM NaCl on filter disks under Ag-AgCl electrodes and 58 $\mu A \cdot cm^{-2}$ for 240 sec to reduce the resistance of the stratum corneum. These same sites were then treated with mixtures of 20 mM MCh and NaCl, with MCh comprising from 0.3%-80% of the total. By changing i, t and %MCh calculated MCh dose (Dmch) was varied from 1-300 $nM \cdot cm^{-2}$. Each site on the same subject received a different dose. Peak sweat rate (SRpk) and number of active glands (AG) were measured as previously described (An. Biomed. Engr. 11:131, 1983). We found (1) SRpk vs log Dmch yielded typical sigmoidal D-R curves, characteristic for each subject, (2) AG also varied hyperbolically with Dmch, but plateaued much sooner than SRpk, (3) adding 1-40 $nM \cdot cm^{-2}$ of atropine sulfate during pretreatment caused incremental displacement of log D-R to the right. (Supported in part by USAMRDC contract DAMD-17-83-C-3181).

29.7

CARDIOVASCULAR RESPONSES TO RHYTHMIC EXERCISE DURING IMMERSION IN WATER AT DIFFERENT TEMPERATURES. C.A. Williams, T.E.Dahms, A.C. Burnham*, and A.R. Lind. Dept. of Physiology, St. Louis University, St. Louis, MO 63104

Six males performed cycle ergometry during head-out whole body immersion in water at 15, 20 and 35°C. Subjects were seated in a tank behind the ergometer that had been modified with a double sprocket so that pedaling occurred below the water but the resistance flywheel was above the tank out of the water. The protocol consisted of a 10min rest period in the water followed by 5min continuous work at 50rpm at 0-3kp belt tensions. HR were measured from the ECG, BP by auscultation, $\dot{V}_{O2}$ from conventional spirometry and cardiac output (C.O.) by the acetylene rebreathing technique. Cardiovascular responses were compared to work done in an empty tank (r.t. 24±0.5°C) with the subjects and ergometer in the same positions. The $\dot{V}_{O2}$, HR, BP and C.O. were similar for work performed in air and water at 35°C, but $\dot{V}_{O2}$, C.O., HR and BP were slightly higher at a given workload in 20° than in 15° water. Ventilatory drive was inhibited during work in progressively colder water. Subjects indicated that shivering was greater in 20° water than in 15° water. A linear relationship was found between C.O. and $\dot{V}_{O2}$ as expected, but a given increment in $\dot{V}_{O2}$ caused less of an increase in C.O. for work done in 15° and 20°water. These changes may reflect the influence of cutaneous thermal receptors and central command rather than alterations in central venous blood volume on cardiovascular function in this situation. (Supported by ONR Grant N00014-77-C-0640)

29.8

CIRCADIAN AND MENSTRUAL CYCLE VARIATIONS IN BLOOD PARAMETERS. L.A. Stephenson, M.A. Kolka and R.R. Gonzalez. J.B. Pierce Fndn. Lab., New Haven, CT 06519

Circadian and menstrual cycle effects on hematological parameters were studied. Four women exercised at 60% peak $\dot{V}O_2$ in 35°C (P_a = 13 torr) for 30 min at 0400 and 1600 h during the follicular (F) and luteal (L) phase. Venous blood samples were drawn during rest and exercise. Hb, Hct, oncotic pressure (COP), plasma protein, epinephrine and norepinephrine concentrations were determined in each sample. Results are shown in Table 1.

	F		L	
	0400	1600	0400	1600
		REST		
PV (ml)	3044	2984	2966	2819
COP (torr)	20.6	22.1	20.4	22.5
TCP (g)	200.1	204.4	197.3	199.0
		EXERCISE		
PV (ml)	2677	2606	2648	2523
COP (torr)	23.9	25.4	25.3	27.2
TCP (g)	197.3	202.8	194.5	196.0

The catecholamines were markedly elevated during exercise, but showed no circadian or menstrual cycle variation. These data indicate that there is a marked hemoconcentration during exercise in a hot environment which is concomitant with a modest loss of protein from the vasculature. The menstrual cycle and circadian variations in PV and COP did not affect performance in this study. However, the higher core temperature which occurs during L is associated with a higher COP and lower PV during exercise.

29.9

INFLUENCE OF TRAINING ON THE METABOLIC AND CARDIAC RESPONSES OF INSULIN-TREATED (I) DIABETIC RATS. J.A. Wegner, D.D. Lund, J.M. Overton, J.C. Edwards, and C.M. Tipton. Departments of Exercise Science and Physical Education and Internal Medicine, Univ. of Iowa, Iowa City, IA 52242.

Recently, (Fed. Proc. 43:870, 1984), we demonstrated the streptozotocin (80 mg/kg, IV)-induced diabetic (D) rats exhibited significant adaptations with training (T). When insulin was injected twice daily (5 U/kg, SC) the $\dot{V}O_2$max values (ml/kg 0.79/min) for the groups were ($\bar{X}$+SE) D-NT=51±3, D-T=57±1; D-I-NT=55±2, D-I-T=55±3, C-NT=60±2, C-T=63±2. All T groups exhibited significant increases in cytochrome oxidase activity when compared to their NT controls. To detect changes in the parasympathetic nervous system, resting heart rates, atrial choline acetyltransferase (CAT) and muscarine receptor and binding (QNB) were assessed. D produced a resting bradycardia, higher CAT levels and QNB binding values; however, T had no significant effect on these parameters. Partial normalization occurred with insulin in these measures and with food and water consumption and urine production. Percent body fat was similar in D and I groups. T when combined with insulin had no significant impact. These results reinforce the concept that hormonally deficient rats can adapt to endurance exercise and indicate that future diabetic studies must measure changes in sympathetic and parasympathetic nervous systems to assess training effect. (Supported in part by Iowa Diabetes-Endocrinology Research Center AM25295-05, the Graduate College and HL-24246.)

29.10

VENTILATORY AND THERMAL EFFECTS OF PROLONGED RUNNING FOLLOWING ACUTE INGESTION OF ACETYLSALICYLIC ACID. Ronald E. DeMeersman,* David C. Schaefer,* and Don M. Fritsch.* (SPON: J.K. Stewart). Virginia Commonwealth University, Richmond, Virginia 23284.

To determine the ventilatory and thermal responses to prolonged running, nine men performed a treadmill exercise of 60 minutes duration after ingestion of a placebo or salicylate (ASA) (3000 mg). Each subject served as his own control and the order of protocols was randomly assigned. Respiratory gases were continuously measured through an on-line indirect calorimetry system. Thermal data were obtained from rectal and three site skin temperatures. A repeated measures analysis of variance yielded the following results. Acute ingestion of therapeutic amounts of aspirin, resulted in near toxic plasma levels of ASA (mean ± S.D. = 27.4 ± 8.1 mg/dl) prior to exercise and significantly altered ventilatory responses. Ventilation volume ($\dot{V}E_{STPD}$), oxygen consumption ($\dot{V}O2_{STPD}$), carbon dioxide production ($\dot{V}CO2_{STPD}$) and breathing frequency in ASA-treated subjects increased 7.6, 4.6, 3.9, and 14.8% respectively over placebo values ($P < .05$). These salicylate-induced perturbations of augmented ventilatory responses occurred without a concomitant significant increase in progressive exercise hyperthermia for the ASA protocol as compared to the placebo. Based on these findings we conclude that acute salicylate ingestion prior to exercise stimulates respiration by a mechanism other than that related to increased body temperature.

29.11

MEASUREMENT OF EXERCISE OXYGEN UPTAKE ($\dot{V}O_2$) USING A BODY PLETHYSMOGRAPH. James D. Anholm,* M. Ramanathan,* R.L. Johnson, Jr. Univ. Texas Hlth Sci Cntr, Dallas, 75235

Breath-by-breath $\dot{V}O_2$ measurements frequently utilize inspired(I) and expired(E) pneumotachographs(PT). Temperature and moisture problems with PT's encouraged us to use a modified flow body plethysmograph (Box). The subject exercises outside of the Box but I and E volumes (V_I, V_E) are separated by collecting V_E in a balloon within the Box. This also allows a confirmatory measurement of V_E. V_E & V_I are measured by sampling pressure(P) changes in the Box at 100 Hz by digital computer. The Box frequency response has been extended to 14-18 Hz by compensating P for gas temporarily "stored" in the Box due to compression: Volume = $\int \dot{V} + K\dot{V}$ (1) where $\dot{V}$ = flow in or out of a Box orifice; K = the fraction of $\dot{V}$ representing gas compression (K$\sim$ .00035). To account for laminar and turbulent gas flow: $P = K_1\dot{V} + K_2\dot{V}^2$ (2) where K_1 = coefficient of laminar flow ($\sim$ -5.19), K_2 = coefficient of turbulent flow ($\sim$ -.0025). Eq. 2 is solved for $\dot{V}$ & the resulting function used in Eq. 1, providing accurate calculation of the instantaneous V_I or V_E. With this method V_E is < 1 % different from the vol. collected in the bag. Mass spectrometer (MS) gas concentrations for O_2, C_{O_2} and N_2 are also sampled at 100 Hz. The MS signal is shifted to account for the time delay between Box P signal and MS signal (measured to be $\sim$ 400 msec). This MS signal is then used to calculate $\dot{V}O_2$ and $\dot{V}CO_2$.

29.12

TORQUE-VELOCITY RELATIONSHIP IN ISOKINETIC CYCLING EXERCISE. G.J.F. Heigenhauser, N. McCartney* and G. Obminski*. McMaster University, Box 2000, Stn. A, Hamilton, Ont., Canada L8N 3Z5.

Seven healthy female subjects performed brief (<10 s) periods of maximal exercise on a constant velocity cycle ergometer over the entire functional range of pedalling velocities, and an isometric contraction with each leg. There was an inverse relationship between peak torque and pedal crank velocity in all subjects; isometric torque was ($\bar{x}$ ± SEM) 19.8 ± 8.3 per cent greater than the torque recorded at the slowest velocity of 11 rpm. The torque-velocity relationship was described best by a single exponential equation: $y = 189.6\ e^{-0.0834x}$, where y is peak torque in N.m and x is crank velocity in rpm. Peak power was a parabolic function of crank velocity; the data were fitted suitably by a second-order polynomial equation: $y = -0.589x^2 + 14.504x + 47.092$. Maximal peak power occurred at crank velocities ranging from 120-160 rpm, when the torque was 0.36 ± 0.06 of the maximal isometric tension. These results demonstrate the importance of recording velocity in measurements of dynamic maximal power.

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29.13

AUTONOMIC REGULATION OF SUBSIDIARY ATRIAL PACEMAKERS DURING EXERCISE IN THE CONSCIOUS DOG. Gregory Pomeroy,* Walter Randall, Jeffrey Ardell. Loyola Univ. Medical Center, Maywood, IL.

Alert, conscious dogs, with indwelling bipolar electrodes on the superior and inferior right atrium and ventricle, were exercised at 4-7 mph (0-8% grade) before and at weekly intervals following sino-atrial node excision (SAN-X). Heart rate (HR), blood pressure (BP), lead II ECG and cardiac electrograms were recorded during control, exercise and recovery periods for SAN intact state and following SAN-X. With SAN intact, cardiac acceleration was immediate and proportional to workload. Atrio-ventricular (A-V) intervals shortened and BP rose 15-20 mmHg during exercise. Immediately following SAN-X (1-7 days), subsidiary atrial pacemaker foci (SAP) were present, but frequently unstable, especially during exercise. Soon thereafter, SAP's stablized demonstrating consistent beat to beat A-V intervals, both at rest and during exercise. Functionally, the SAN-X animal exhibited prompt but distinctly attenuated cardiac acceleration during exercise. Combined timolol-atropine blockade increased HR at rest and significantly attenuated the tachycardia accompanying exercise in the SAP animal. Moreover, autonomic regulation was consistent throughout the maturation and stablization of the SAP foci even immediately following SAN-X, and resulted in maintenance of adequate cardiac rate augmentation in response to dynamic exercise. (Supported by NIH grants HL27595, HL27664 and HL28205)

29.14

ACUTE COLD STRESS RESPONSE IN AMENORRHEIC AND CONTROL WOMEN AS COMPARED TO MEN. J.P. Van Dijk*, M. Viswanathan*, T.E. Graham, J. George*. Human Biology and Zoology, University of Guelph, Guelph, Ontario, Canada. N1G 2W1

If thermal-metabolic sex differences in the cold are morphologically based (eg. %Body Fat(BF), Mass(kg)), amenorrheic (AW) women should be more extreme in response than menstruating women (CW). Lightly clad men (M;n=6;$\bar{x}$=8.9%BF;$\bar{x}$=74.1kg),CW (n=6;$\bar{x}$=21.5%BF;$\bar{x}$=59.8kg) and AW(n=4;$\bar{x}$=17.4%BF;$\bar{x}$=53.1kg) performed 2 20-min. workloads (I=30%$\dot{V}O_2$ max;II=60%$\dot{V}O_2$ max) and an exhaustive workload (III=90%$\dot{V}O_2$ max) at +5.0°C. Skin and rectal temp. (T), $\dot{V}O_2$, R, Blood Glucose (BG) and Lactate (BL) were monitored. Thermal responses suggested 3 distinct groups (M, CW and AW); Trectal was consistently highest in CW and lowest in AW($p<0.05$) and Tskin and Tbody were highest in M and lowest in AW during work II ($p<0.05$). In contrast, only 2 groups, M and W (CW+AW) existed metabolically. BG tended to be higher in M; during work III BG was 5.2mM in M and 3.7mM in W ($p<0.10$). BL was 10.6mM in M and 6.3mM in W ($p<0.05$), despite the same %$\dot{V}O_2$ max and work III duration. Apparently, W were more conservative in BG use and a consistent trend for lower R values supports this theory. Morphology was not the dominant factor since thermal responses were not consistently the least in M and greatest in AW and metabolically AW and CW were not different. Physiological differences (eg. endocrine) may have a dominant role.

Supported by Natural Sciences & Engineering Research Council of Canada

29.15

OXYGEN UPTAKE KINETICS IN TRAINED ATHLETES DIFFERING IN $\dot{V}O_2$ MAX. Scott K. Powers, Stephen Dodd*, and Ralph Beadle*. Applied Physiology Laboratory, Louisiana State University, Baton Rouge, La. 70803

Previous work has shown that when $\dot{V}O_2$ kinetics are compared for endurance-trained athletes and untrained subjects, the highly trained athletes have a faster response time. However, it remains to be determined whether the more rapid adjustment of $\dot{V}O_2$ toward steady state in athletes is due to genetic differences or training adaptation alone. Therefore, the purpose of these experiments was to compare the time course of $\dot{V}O_2$ kinetics at the onset of exercise in athletes with similar training routines but who differ in $\dot{V}O_2$ max. Ten subjects ($\dot{V}O_2$ max range 50-70 ml · kg^{-1} · min^{-1}) performed 6 minutes of cycle ergometer exercise at $\sim$ 50% $\dot{V}O_2$ max. Ventilation and gas exchange were monitored by open circuit techniques. The data were modeled with a single component exponential function incorporating a time delay, (T_D):

$$\Delta\dot{V}O_{2_t} = \Delta\dot{V}O_{2_{ss}}(1-e^{-(t-T_D)/\tau}).$$

Kinetic analysis revealed a range of $\dot{V}O_2$ half-times from 21.6 to 36.0 S across subjects with a correlation coefficient of $r = .780$ ($p < 0.05$) between $\dot{V}O_2$ max and $\dot{V}O_2$ half-time. Given the belief that $\dot{V}O_2$ max is largely determined by genotype, these data suggest that genetic factors make a significant contribution to the rapidity of O_2 uptake at the onset of exercise.

29.16

ACCURACY OF IMPEDANCE CARDIOGRAPHY (IC) DURING MAXIMAL EXERCISE TESTING. K. Teo,* M. Hetherington,* R. Haennel,* T. Kappagoda, and P. Greenwood* Univ. of Alberta, Edmonton, Alta. Can.

Impedance cardiography (IC) is a non-invasive method of measuring cardiac output (CO). This study was undertaken to determine the reproducibility of these measurements during maximum exercise. The technique (Minnesota Impedance Cardiograph 304A) was compared first with the Fick Technique in 15 cardiac patients during routine catheterization over a range of 4 to 18 L/min and shown to have no systematic error ($r=0.9$ $p<0.01$). The short term reproducibility was assessed in 5 healthy males while they were in a steady state at rest and exercise at 80 and 130 W. The coeff. of variation was < 5%. Six healthy trained males (age 25.8 ± 2.1 yrs, SEM) underwent maximum exercise tests twice, one week apart on a bicycle ergometer with simultaneous recordings of CO and oxygen uptake (VO_2) at rest and during each 3 minute stage of exercise. IC recordings were made during breath holding at normal end-expiration. Stroke volume (SV) and CO were derived from these recordings. Highly significant correlations were obtained in the CO ($r=0.98$), SV ($r=0.84$) and VO_2 ($r=0.98$) between the 2 tests. Mean maximum CO was 27.0 ± 1.2 l/min (SEM) and mean maximum VO_2 was 4.4 ± 0.2 l/min. These results show that the measurements of CO were reproducible over 1 week. These results indicate that IC is a non-invasive technique which is as accurate as invasive techniques and could be used for maximal exercise testing.

Supported by I.O.D.E. (Edmonton)

29.17

CARDIOPULMONARY RESPONSES OF PONIES TO A STANDARD EXERCISE TREADMILL TEST. W.L. Sexton*, D.R. Argast*, and H.H. Erickson. Kansas State University, Manhattan, KS 66506.

Eight untrained ponies, ages 3 to 8 years, 156±56 kg., were subjected to a standard exercise test (SET) on a large animal treadmill at 7°. Running speed was increased in five five min. increments from 1.0-3.4 $m \cdot sec^{-1}$. During the SET and recovery we recorded ECG, aortic pressure (P_{ao}), right ventricular pressure (P_{rv}) and dP/dt, pulmonary artery pressure (P_{pa}) and flow velocity ($\dot{Q}_{pa}$), and blood temperature in the pulmonary artery (T_{pa}). Arterial samples were taken for lactic acid (LA), hematocrit (Hct), hemoglobin (Hb), and blood gases (PaO_2, $PaCO_2$).

Between rest and 3.4 $m \cdot sec^{-1}$, heart rate increased from 44 to 204 $b \cdot min^{-1}$. Mean P_{ao} decreased initially, but returned to the rest level of 116 mm Hg. Mean P_{rv} increased from 19 to 49 mm Hg, while dP/dt increased from 400 to 2300 mm Hg$\cdot sec^{-1}$. Mean P_{pa} increased from 20 to 38 mm Hg and mean $\dot{Q}_{pa}$ increased from 13 to 94 $cm \cdot sec^{-1}$. Hct increased from 27.6 to 40.0 and Hb from 8.9 to 13.4 gm%. Blood lactate rose from 8.3 mg% at rest to 93.0 mg% during exercise. PaO_2 remained constant at 97 torr while $PaCO_2$ fell to 27 torr from a rest of 45 torr. T_{pa} increased 2.6C during exercise. All parameters except lactic acid, returned to near resting levels within 16 minutes post-exercise. This SET is presently being used to evaluate fitness prior to and following specific training programs to determine their relative efficacy. (Supported by USDA 55604-0374).

29.18

EVOLUTION OF THERMOREGULATION IN RATS. P. M. Zavos,* E. C. Rowe* and D. L. Spencer.* (SPON: S. J. Legan). Emporia S. Univ. and Univ. Ky., Lexington, KY 40546.

The objective in this study was to investigate the evolution of thermoregulation in rats (Rattus norvegicus). Forty-five animals of various age groups were used in this investigation. These age groups (in days) with the corresponding number of animals used per group (in parenthesis) were: 1) 6-7 (n=10), 2) 10-11 (n=10), 3) 14-15 (n=10), 4) 20-21 (n=10), 5) 60-70 (n=5). The animals were exposed to a 5°C environment by being placed in a specially designed household refrigerator. Measurements of body temperature (intra-abdominal), heart and metabolic rates were obtained throughout the total time of cold exposure at 15-minute intervals. The results showed a progressive pattern of thermoregulation during the maturation of the suckling rats. The first evidence of the ability of the suckling rats to partially counteract the severe low temperature stress was found in age group 4. All three younger groups showed statistically significant differences from age group 4 in all the variables under study ($P<.05$). Furthermore, age group 4 showed some stability in O_2-uptake, heart rate and intra-abdominal temperature during the first half hour of cold exposure. The response patterns of age group 4 to cold exposure were similar to those of age group 5 which are recognized thermoregulators, suggesting that suckling rats begin to thermoregulate at age 20-21 days old.

29.19

STRAIN DIFFERENCES IN CARDIOPULMONARY AND HEMATOLOGICAL RESPONSES TO HYPOXIA IN MICE. G.L. Sardella*, G. Birchard* and L.C. Ou, Department of Physiology, Dartmouth Medical School, Hanover, NH.

CF_1 and CAF_1 strains of mice differ greatly in their polycythemic response to severe hypoxia and may similarly differ in the cardiopulmonary responses. The present study was to test this possibility and to evaluate the roles of tissue hypoxia and erythrocytic 2,3-DPG in these strain differences. PO_2 of the subcutaneous gas pocket was used to estimate tissue oxygenation. Two groups of 10 animals each of both strains were exposed to sea level (SL) pressure and 18,000 ft for 30 days. At the end of exposure, PO_2 of the gas pocket of each animal was analyzed. The animals were then sacrificed and the weights of total ventricle (TV), right ventricle (RV), hematocrit (Hct), and 2,3-DPG were measured. There were no strain differences in all cardiopulmonary and hematological parameters at SL. The mean Hcts of the chronically hypoxic (CH) CF_1 and CAF_1 mice were 76 and 57%; the percent increase in TV and RV to body wt ratios in CF_1 were 30 and 190, as compared to 0 and 140 in CAF_1 and there were no significant strain differences in tissue PO_2 and 2,3-DPG under SL and CH conditions. The data suggest that 1)the excessive polycythemic response to hypoxia in the CF_1 is associated with an exaggerated cardiopulmonary response, and 2)neither tissue oxygenation nor erythrocytic 2,3-DPG play primary roles in the exaggerated cardiopulmonary and hematological responses to hypoxia in the CF_1 mice. (Supported by NIH grant HL 21159)

29.20

DO SEX HORMONES ACCOUNT FOR THE MALE (M)-FEMALE (F) DIFFERENCES IN THE SUSCEPTIBILITY OF RATS TO CHRONIC HYPOXIA? C. Mulligan*, G.L. Sardella*, L.C. Ou, T. Brinck-Johnsen* and R.P. Smith* Depts. of Physiology, Pathology and Pharmacology and Toxicol., Dartmouth Medical School, Hanover, NH.

On chronic exposure to severe hypoxia, M and F rats of the Hilltop Sprague-Dawley strain developed comparable cardiopulmonary (CP) responses, but distinctly differed in their susceptibility to mortality. Castration and ovariectomy were employed to reduce sex hormones. Four groups of 6 to 10 animals of both M and F were studied: sea level (SL) and high altitude (HA) intact and ablated groups. One week after surgery, the animals were exposed to SL pressure or to 18,000 ft simulated altitude for 30 days. At the end of exposure, right ventricular systolic peak pressure (RVPP), BP, weights of the total ventricle (TV), right ventricle (RV), hematocrit (Hct) and plasma estradiol and testosterone were determined. There was no sex difference in any CP parameter at SL. HA exposure greatly and comparably elevated the RVPP, TV and RV to body wt ratios in both sexes. All F survived but 67% of the M died. Castration did not significantly change any of the CP parameters or the mortality rate. Ovariectomy significantly elevated the RVPP, TV and RV to body wt ratios and the Hct at HA and one out of 6 Fs died. M sex hormones alone did not seem to cause M susceptibility to HA. The aggravated CP and hematological responses to hypoxia with minimal mortality following ovariectomy may be due to the suppressive effect of F hormones on the Hct. (Supported by grants HL 21159 and HL 14127)

29.21

DYNAMIC CHARACTERISTICS OF THE PULMONARY PRESSOR RESPONSE TO ACUTE HYPOXIA (PPRAH) IN TWO STRAINS OF RATS. L.C. Ou, G.L. Sardella*and N. Hill* Dept. of Physiology, Dartmouth Medical School, Hanover, NH and New England Medical Center, Boston, MA.

On chronic exposure to hypoxia (18,000 ft, or 10.5% O_2), Hilltop (H) strain of Sprague-Dawley rats develops severe pulmonary hypertension (PH) whereas the Madison (M) strain develops only moderate PH. The PPRAH was tested in fully awake animals before, during 30 days of, and after hypoxic exposure to evaluate the relationship between the PPRAH at sea level (SL) and the chronic hypoxia (CH)-induced PH, and to determine the dynamic characteristic of PPRAH in these two strains. In response to AH, the mean pulmonary arterial blood pressure (PAP) of the SL M rats rose from the control value of 16 mmHg to 29 (up 80%) whereas those of the H rats increased from 16 to 21 (up 30%). 24 hr of hypoxia greatly diminished or abolished the PPRAH in both strains. During hypoxic exposure, the rise of the mean PAP was consistently greater in the H than in the M rats; in general, there was only a minimal change in the mean PAP in both strains when the animals were made acutely normoxic. PPRAH, similar to or greater than the SL controls, was consistently demonstrated at varied intervals during post-hypoxic recovery. The data suggest that 1)there was no correlation between the PPRAH at SL and CH-induced PH, 2)PPRAH was blunted after 24 hr of hypoxia and remained as long as hypoxia continued and even shortly after hypoxia, 3)PPRAH gradually returned to, or exceeded the SL controls during post-hypoxic recovery. (Supported by NIH grant HL-21159)

29.22

OXYGEN DELIVERY IN HYPOTHERMIA. Anthony Warley* and Guillermo Gutierrez. Univ. of Texas Medical School, Houston, Tx. 77025.

Hypothermia produces a decrease in metabolic rate which may be beneficial under conditions of reduced oxygen (O_2) delivery. A further effect of hypothermia is to increase the affinity of hemoglobin (Hb) for O_2 and it is generally believed that this interferes with release of O_2 to the tissues. Recent theoretical and experimental evidence, suggests that increased affinity of Hb for O_2 may be of benefit under conditions of extreme hypoxemia. Our hypothesis is that the hypothermic animal continues to extract O_2 at lower arterial (PaO_2) and mixed venous (PvO_2) oxygen tensions that the normothermic animal. Fourteen dogs were anesthetized and artificially ventilated. Seven animals served as controls, (T = 37.5±0.5°C) and were subjected to progressive hypoxemia until cardiac arrest. Measurements of PaO_2 and PvO_2, Hb saturations, and cardiac output were obtained. The other seven animals were cooled to 30±0.5°C and also subjected to progressive hypoxemia. At the time when the animals reached their maximum O_2 extraction ratio, (E.R.=consumption/O_2 delivery), the following data were obtained (± SEM).

Temp (C)	P_{50} (mmHg)	E.R. (%)	PaO_2 (mmHg)	PvO_2 (mmHg)	Ca (vol %)	Cv (vol %)
37	30.1±0.87	62±3.3	17.6±1.29	8.6±0.70	3.34±.274	1.22±.074
30	19.6±0.75	57±3.2	8.30±0.47	4.0±0.28	2.34±.031	1.10±.105
	p<.01	NS	p<.01	p<.01	p<.01	NS

These results support our hypothesis, since significant differences exist in PaO_2's and PvO_2's between the hypothermic and control animals at a similar point of maximum extraction ratio.

29.23

EFFECT OF HYPERTHERMIA ON PULMONARY CIRCULATION IN THE RAT. H.M. Frankel and B.J. McGarry*. Bureau of Biological Research, Rutgers Univ., New Brunswick, N.J. 08903

Pulmonary arterial pressure (PAP), systemic arterial pressure (MAP), and cardiac output (CO) were measured in anesthetized rats at body temperatures (Tr) of 38-41°C. Tr was increased by exposure to an environmental temperature of approx. 36°C. Pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR) were calculated at Tr's of 38, 39, 40 & 41°C. At normothermia mean PAP and MAP were 19 and 135 mmHg, respectively, and did not change significantly when environmental temperature (Te) was changed from approx. 23°C to 36°C. During hyperthermia mean PAP was approx. 20 mmHg at Tr of 38 to 39°C and approx. 12 mmHg at Tr of 40 & 41°C; a significant decrease from the values at 38 & 39°C. MAP did not change significantly with increased Tr. Mean CO was increased significantly when the rats were placed in the temperature chamber at 36°C. However, CO was not significantly changed as Tr increased from 38°C to 41°C. PVR and and SVR were significantly decreased when the rats were exposed to a Te of 36°C. In addition, PVR was significantly less at a Tr of 40 & 41°C compared to a Tr of 38 & 39°C. However, SVR did not show a significant change with increased Tr while the animals were in the temperature chamber. We conclude exposure to high environmental temperature as well as increased body temperature can initiate reflex changes in pulmonary circulatory dynamic in the anesthetized rat. (Supported by the Busch Memorial Fund.)

29.24

EFFECTS OF FLUOSOL ON HEAT STROKE INDUCED RATS. Huey Green McDaniel and Huey Barret McDaniel. V.A. Medical Center and University of Alabama in Birmingham, Birmingham Al. 35233.

Can Fluosol (FC-43) be used to increase oxygen retention, blood pressure, and blood volume and to decrease blood viscosity in heat stroke victims, allowing survival of extreme temperatures for longer periods of time? Six anesthetized rats were injected, intraperitoneally, with 20 ml of FC-43, suspended with Pluronic (F-68) by sonication. Five anesthetized rats served as controls. One group of rats was heated until reaching or surpassing heat stroke temperature (39.5°C) and then returned to normal body temperature (34.5°C) for observation. The remaining rats were heated to progressing predetermined temperatures upon which blood-oxygen levels were measured and hematocrits were taken. Rats treated with Fluosol were able to survive temperatures in excess of 43.6°C. Control rats died at lower temperatures. Rats treated with FC-43 had 30.9% higher blood-oxygen content than untreated rats. Blood hematocrits were elevated with increasing body temperatures. There were no signifigant differences in hematocrit between Fluosol treated and untreated rats. Treatment with the perflurochemical signifigantly increased blood-oxygen levels and the rate of survival of heat stroke as compared to rats left untreated.

CARDIAC DYNAMICS

30.1

INVASIVE VERSES NONINVASIVE MEASUREMENT OF LEFT VENTRICULAR EJECTION TIME AND CARDIAC OUTPUT. Robert J. Demeter*, Steven A. Hamburger*, Phillip D. Toth*, William V. Judy. Department of Medical Research, Methodist Hospital of Indiana, Inc., Indianapolis, IN 46202.

Left ventricular ejection times (LVET) measured invasively from the ascending aortic pressure (AP) waveform and noninvasively from the change in impedance (Z) waveform and first derivative of the impedance signal (dZ/dt) were simultaneously recorded in 11 male hounds (20-25 kg). Cardiac output (CO) measurements also were determined via thermodilution (T) and impedance cardiography (ZCG) simultaneously. The hounds were anesthesized with thiopental (30 mg/kg) and intubated to breath room air. A Millar transducer tipped catheter was positioned in the ascending aorta, and a Swan-Ganz thermodilution catheter was positioned in the pulmonary artery. The onset of the AP waveform and Z waveform along with the ejection point (E point) of the dZ/dt waveform were found to occur simultaneously. The dicrotic notches (termination of LVET) of the AP waveform and the Z waveform along with the most positive peak of the dZ/dt waveform occurred simultaneously. A summary of left ventricular ejection times, heart rates (HR) and cardiac outputs were as follows:

	LVET (AP)	LVET (dZ/dt) (Sec)	LVET (Z)	CO (T) (L/Min)	CO (ZCG)	HR (bpm)
X±SEE	.148±.002	.146±.002	.147±.002	4.61±.002	4.45±.079	176±1.15

Ejection time correlations between the AP and Z and dZ/dt methods were r=0.99 and 0.98, respectively. The correlation coefficient between the Z and dZ/dt measured LVET was r=0.98. Cardiac output comparisons were almost identical with r=0.96. In summary, accurate determinations of LVET and CO were determined noninvasively by impedance cardiography in comparison to the ascending aortic pressure waveform and thermodilution techniques in this group of hounds.

30.2

INTRAVENTRICULAR PRESSURE-IMPEDANCE DIAGRAMS(DPZ) TO DETERMINE THE END-SYSTOLIC POINTS LOCUS. Julio C. Spinelli, Oscar E. Clavin, Max E. Valentinuzzi. Bioingeniería. Instituto Superior Investigaciones Biológicas. CONICET-UNT. Tucumán, Edmundo I. Cabrera, Marcelo R. Chatruc and Ricardo H. Pichel. Fundación Favaloro. Bolís 453, Buenos Aires (1078), Argentina.

By means of tetrapolar intraventricular impedancimetric measurements and modifying the aortic hydraulic impedance with a volume unit step (afterload increase with a balloon), we obtained the geometric locus of the end-systolic pressure-admittance points (PES-YES) from the beat to beat DPZ. Six experiments in five mongrel dogs (21.6 kg, SD 2.5, morphine, sc, 20 mg/kg + pentobarbital, iv, 10 mg/kg) were carried out under control conditions C and after a slow infusion (4 ug/kg·min) of epinephrine E. In C the PES-YES points fell in all cases on a straight line ($r > 0.850$). After E linearity was good in four experiments ($r > 0.800$). All animals showed displacements of the regression lines after E with respect to C. However, the direction of the shifts was not always consistent: three dogs yielded an upward-leftward shift, one showed a crossing point between the two regression lines with an increase in slope after E; in the remaining two experiments (same dog in different days), the post E regression lines were displaced downwards and rightwards. Five out of the six experiments increased the the slopes of the lines after E. We concluded: the method could produce the PES-YES locus in patients subjected to cardiac catheterization and these loci would be altered by inotropic interventions. (Grants from CONICET, UNT, Fundación Favaloro)

30.3

EFFECT OF AGE AND SEX ON HEART RATE AND IMPEDANCE-DERIVED ESTIMATES OF STROKE VOLUME INDEX AND THORACIC BLOOD VOLUME DURING VALSALVA MANEUVER. C.J.Porth, J.J.Smith, C.V.Hughes*, M.J.Ptacin*, L.Groban*, J.A.Barney*. Sch. of Nrsg.,Univ. Wis. Milwaukee, Milwaukee,WI 53211, Dept. of Physiol., Med. Coll. of Wis., Milwaukee, WI 53226, V.A. Med. Ctr., Wood, WI 53193.

The purpose of this study was to determine the effect of age and sex on heart rate (HR) and impedance-derived estimates of stroke volume index (SVI) and thoracic blood volume (TBV) via baseline transthoracic impedance (Z_0) during supine 15 sec, 40 mm Hg Valsalva maneuver (VALS). 4 groups of males (M) and females (F) were studied:YM(8 M,20-29yrs), OM(8 M,40-49yrs), YF(9 F,20-29yrs) and OF(9 F,40-49yrs). Control and maximum % change from control (%Δ) at the end of strain (mean±SEM) were:

	HR(b/min) control	HR(%Δ) strain	SVI(ml/m²) control	SVI(%Δ) strain	$Z_0(\Omega)$ control	Z_0(%Δ) strain
YM	60.8±1.9	57.4±9.5	44.1±3.0	-51.8±6.7	23.5±0.8	3.4±0.6
OM	60.9±1.8	41.4±9.7	41.0±2.1	-45.0±6.7	23.0±0.8	3.8±0.9
YF	66.1±2.9	36.4±7.3	44.1±3.6	-47.6±5.4	27.3±0.8	7.8±0.8
OF	64.9±1.7	49.7±4.6	45.0±2.3	-63.1±4.2	28.8±1.0	6.6±1.5

The OM in this study had lesser increases in HR and decreases in SVI as compared to YM, a finding that was reversed in OF. These data suggest that during VALS strain: a) the age effect on HR and SVI is different in M and F, and b) that the decrease in TBV is greater in F of both age groups. (Supported by a NRSA nurse fellowship award, NHLBI grant AGO 3064 and the Veterans Administration)

30.4

CARDIAC RESPONSES TO GRAVITATIONALLY-INDUCED CHANGES IN VENOUS RETURN. G.N. White*, C.F. Knapp, D.C. Randall, and J.M. Evans. Univ. of Kentucky, Lexington, KY 40536.

Venous return (VR) was inhibited in chronically instrumented, Innovar-sedated dogs (n=4) by subjection to +2Gz acceleration. After a 3 min. control period, the +2Gz acceleration was suddenly removed. Left ventricular (LV) volume was calculated continuously from major and minor ultrasound axes measurements. The LV pressure-volume ratio (P/V) and d(LVP)/dt were also recorded. Dogs with both α and β blockade (phenoxybenzamine + propranolol) responded to the shift in VR with an increased LV volume (systolic 6.3 ± 3.3 ml (S.D.), diastolic 12.6 ± 6.4 ml) within 6 heart beats. Neither P/V nor d(LVP)/dt increased. Although α and β adrenergic mechanisms are not expected to be effective within this time, unblocked P/V and d(LVP)/dt were variable. However, like blocked response, unblocked LV volumes did consistently increase. From 10 to 60 sec. following the shift, no increases were observed in P/V or d(LVP)/dt for either group. Since increased LV volume with no increase in contractility resulted from the shift in VR in the blocked state, it is suggested that the heart relies upon the Frank-Starling mechanism to match cardiac output to VR during gravitationally-induced translocations of blood. In the unblocked state, the response is a combination of Frank-Starling and other mechanisms. Data do not suggest that contractility increases to relieve the engorged ventricle. (Supported by NIH grant HL19343 and AFOSR 80-0039.)

30.5

DETERMINANTS OF LEFT-VENTRICULAR DIMENSIONS AND DYNAMICS. Calvin R. Maurer, Jr.* and David M. Regen. Vanderbilt University Medical School, Nashville, TN 37232

With the aim of refining interpretation of cardiologic data, we developed a model showing how average left-ventricular dimensions and dynamics depend on average demands (stroke volume, systolic pressure) and average myocardial properties (growth ability, contractility). It involves three equations: one expressing stretch normalization, one expressing stress normalization, one translating muscle dynamics to chamber dynamics. It predicts eccentric hypertrophy and increased volume-displacing ability in response to increased volume demand, concentric hypertrophy and increased pressure-making ability in response to increased pressure demand, synergism between growth ability and contractility as regards performance and midwall dimensions, eccentric hypertrophy in response to low contractility, dilation in response to low growth ability, marked reduction of cavity volume and volume-displacing ability incident to slight exess myocardial mass. Comparing predictions with clinical experience suggests that wall thickening in the adult is typically accompanied by reduced contractility. Supported by Vanderbilt Univ. Res. Council and National Research Service Award T32-HL-07411.

30.6

REGIONAL MYOCARDIAL VOLUME ALTERATIONS INDUCED BY BRIEF REPEATED CORONARY OCCLUSIONS IN CONSCIOUS DOGS M. Fujita*, D. McKown*, M. McKown*, D. Franklin. Dalton Research Center, Univ. of Missouri, Columbia, MO 65211

Thirteen dogs were instrumented for measurement of regional endocardial segment lengths in areas perfused by the circumflex coronary artery (CCA) and anterior descending coronary artery (LAD), CCA flow and left ventricular pressure. A pneumatic occluder was implanted around the CCA. After recovery from surgery, 2 min CCA occlusions were repeated hourly for 17±8 (SD) days (182±74 occlusions). In CCA zone, end diastolic segment length increased 3.8±3.9% ($P<0.025$, n=9), segment systolic shortening increased from 21.3±5.4% to 23.2±5.3% ($P<0.01$) and end diastolic wall thickness increased 1.5±1.6% ($P<0.025$, n=9). In LAD zones, end diastolic segment length decreased 1.3±3.9% (n.s., n=8). Heart rate, systolic and end diastolic pressure and dP/dt were unchanged. Thus, chronically repeated, brief ischemia episodes induced sustained regional myocardial elongation and thickening in the ischemic zone. These findings suggest an increase in myocardial volume, perhaps in response to the periodic stimulus of increased systolic wall stress associated with regional ischemia.

30.7

HUMAN CARDIOVASCULAR RESPONSES FOLLOWING ALCOHOL CONSUMPTION STUDIED WITH THE DIVING REFLEX. G. Fall*, R. S. Pozos*, L. Beck* and L.E. Wittmers Jr* (SPON: P. ROYCE). Univ. of Minnesota Duluth School of Medicine, Duluth MN. 55812

In six human volunteers the cardiovascular responses associated with the diving reflex were elicited by face immersion in 4°C water. The immersion was done before and after alcohol consumption (blood alcohol levels of 0.1 g%). Heart rate (beat to beat), blood pressure (sphygmomanometer) and stroke volume (impedance cardiography) were continuously monitored before and during the immersion.
Heart rates following alcohol consumption were significantly higher. This was true prior to and during the dive. Although in both cases the face immersion resulted in an equivalent fall in heart rate. Mean arterial blood pressure following alcohol comsumption was not different from control. However upon immersion the post alcohol blood pressures did not rise to the same extent as in the control state. Stroke volume prior to face immersion was the same pre and post alcohol consumption . However, upon face immersion, the stroke volume increased in the controls and decreased post alcohol consumption.
Supported in part by Minnesota Sea Grant NA 82AA-D-00039 Project #R/S-2

30.8

THE MAXIMUM BLOOD PRESSURE (BP) RESPONSE TO AN INCREASE OF INTRACRANIAL PRESSURE (CUSHING RESPONSE) IS LESS THAN THE MAXIMUM BP INDUCED BY EPINEPHRINE IN NEONATAL RABBITS. Christopher S. Ogilvy* and Arthur B. DuBois. The John B. Pierce Foundation and Yale Univ., New Haven, CT 06519.

The Cushing response of neonates has not been described in detail. To test it, we infused normal saline in stepwise increments at 20 second intervals into the subarachnoid space of 5 two day old neonatal and 7 adult rabbits anesthetized with urethane. Hypertension, bradycardia and slower breathing occured in both adults and neonates. In adults BP increased from a control level of 94/76 mm Hg (mean 85, SE 5) to a maximum of 199/161 (mean 179, SE 4). Intra-arterial injection of 1.0 mg epinephrine was used to produce maximal sympathetic response and produced a BP of 199/166 (mean 182, SE 7, not significantly different from the BP produced by the increased ICP). In neonates, the control BP was 33/19 (mean 26, SE 1). The maximum BP during increased ICP was 58/32 (mean 45, SE 6). Intra-arterial injection of 0.1 mg epinephrine alone raised the BP to 88/44 (mean 66, SE6). This value is significantly higher than the BP maximum observed with increased ICP (p 0.05). Thus, the endogenous maximal sympathetic stimulation during the Cushing response did not elicit as great a BP increase as did the exogenous maximal sympathetic response, in the neonate, probably because of an immature adreno-medullary axis (Padbury, et al., Am. J. Ob. Gyn. 141: 199-204, 1981). A study of the catacholamine levels in the blood is in progress.(NIH grant HL 17407)

34.1

BONE LOSS OF ESTROGEN DEFICIENCY RESULTS FROM OSTEOBLASTIC DYSFUNCTION - A DEFECT REVERSED BY $1,25(OH)_2$VITAMIN D_3. H.H. Malluche, S. Okamoto*, H. F. DeLuca, M.C. Faugere*. Div. Neph., Bone, Min. Metab., Univ. of Kentucky, Lexington, KY 40536, Dept. Biochem., Univ. of Wisconsin, Madison, WI 53706.

Twelve rats were oophorectomized (OOX), 6 of these received daily subcutaneous injection of 135 pmol of $1,25(OH)_2$Vitamin D (1,25) for 14 weeks starting 38 weeks after OOX. Nine rats were sham operated, 5 of these received the same treatment with 1,25. There were no differences in serum calcium and phosphorus among all groups of experimental rats. OOX resulted in a decrease in cancellous and cortical bone mass, a fall in osteoid volume and osteoid surface, and reduction of growth plate width. However, number of osteoblasts was unchanged after OOX. There were no differences in number of osteoclasts and osteoid seam width among all groups of rats. This indicates that bone loss after OOX is caused by decreased bone forming activity of osteoblasts and not by enhanced bone resorption. Administration of 1,25 to sham operated rats produced an increase in cancellous and cortical bone mass without a change in osteoid volume, osteoid surface or number of osteoblasts. Growth plate width was normal after administration of 1,25. The data show that 1,25 reverses--at least in part--the osteoblastic dysfunction associated with estrogen deficiency, resulting in an increased bone formation per osteoblast.

34.2

ENDOGENOUS CALCITONIN IS NOT A LONG-TERM MODULATOR OF EFFECTS OF PARATHYROID HORMONE ON BONE. M.C. Faugere*, H.H. Malluche, Univ. of Kentucky, Div. Neph., Bone, & Min. Metab, Lexington, KY 40536.

There is a dominating trend in the literature for the concept that calcitonin (CT) antagonizes effects of parathyroid hormone (PTH) on bone. This was challenged by studying 16 dialysis pts with various CT and PTH levels. Also, 2 pts with normal renal function and high CT from medullary carcinoma of the thyroid were studied, one with high PTH, the other with normal PTH. Bone histology was correlated with CT and PTH in all pts (Σ) and separately in pts without bone aluminum (Al-). In uremic pts CT levels ranged from 0 to elevated and no correlations were found between CT and bone histology or CT and PTH. However, PTH correlated well with bone histology.

	CT		PTH	
	Σ r	Al(-) r	Σ r	Al(-) r
Bone-osteoclast interface	-.12	.15	.63*	.72**
Osteoid-osteoblast interface	.20	.15	.63*	.86**
Doubly labeled osteoid	.20	.15	.58	.69*
Bone formation rate	.24	.21	.64*	.72**
Bone resorption rate	.14	-.11	.76**	.68*

* $p < 0.01$ ** $p < 0.001$

Comparisons of the 2 pts with high CT and normal vs high PTH reveal signs of excess PTH on bone in the latter. These findings argue against the notion that CT is a major longterm modulator of PTH effects on bone in uremia.

34.3

HYPERCALCEMIA OF MALIGNANCY: BONE RESORPTIVE ACTIVITY FROM HUMAN TUMOR CELL LINES. P. Sammon, H. Pauley, K. Bailey, J. Flueck and D. Cohen. University of Kentucky Colleges of Medicine and Dentistry and VA Medical Center, Lexington, KY. 40536

Hypercalcemia associated with malignant solid tumors is primarily due to excessive resorption of calcium from bone. We have employed a modified fetal mouse long bone resorption assay to assess the bone resorptive properties of cell lines derived from patients with malignancy associated hypercalcemia. Spent media from these cell lines demonstrated significant bone resorption at dilutions of 1:2,1:4 and 1:9. Native Parathyroid hormone (PTH) was not detected in the media. Spent media from these cell lines were chromatographed on a column of ACA-54 Ultrogel. Fractions were lyophylized and assayed for bone resorption activity. Two major active peaks were noted, the first, just after the albumin but before bPTH 1-84 (MW 9,500). The second peak eluted between bPTH 1-84 but before bPTH 1-34. Further studies demonstrated that the bone resorption activity could also be stimulated in these cell lines by: the tumor promotor Phorbol Myristate Acetate(PMA), the lectins Phytohemagglutinin(PHA), Conconavilin A (ConA) and Lipopolysaccharide (LPS) as well as the media suppliment 'Its' (Insulin, Transferin and Selenium). This data indicates that the bone resorption activity secreted from cells derived from tumors of patients with hypercalcemia associated with malignancy is distinct from native PTH and is also stimulated by PMN, PHA, ConA, LPS and Its.

34.4

INSULIN AND GLUCAGON SECRETION IN HAMSTERS WITH MONOSODIUM GLUTAMATE-INDUCED LESIONS OF THE HYPOTHALAMIC ARCUATE NUCLEUS. J.L. Sartin, A.A. Lamperti* and R.J. Kemppainen. Auburn Univ., AL 36849 and Temple Univ., Philadelphia, PA 19140.

Monosodium glutamate (MSG) will produce specific lesions of the hypothalamic arcuate nucleus (ARC) which result in glucose intolerance in hamsters. Golden hamsters were injected with MSG (8 mg/g BW) on day 8 of the neonatal period and controls were injected with saline. At 3 months of age, oral glucose tolerance tests were performed (glucose: 180 mg/100 g BW). Hamsters were anesthetized with ether and a single blood sample taken from the portal vein. Blood was placed in chilled tubes containing EDTA and Trasylol, centrifuged and plasma stored frozen. Glucose was assayed by the glucose oxidase method and immunoreactive insulin (IRI) and glucagon (IRG) by RIA. Data were analyzed by analysis of variance and Students t-test. No differences were seen in plasma glucose between MSG treated and control hamsters. IRI was higher ($P < 0.05$) in MSG treated hamsters 60 min. after glucose while IRG levels were significantly higher ($P < 0.05$) in MSG treated hamsters at 30 min. after glucose. However, molar IRI/IRG ratios did not differ at any time point, which may account for the lack of differences in plasma glucose. These data suggest a role for the ARC in the regulation of pancreatic function.

34.5

AMINO ACID DISTRIBUTION IN STREPTOZOTOCIN(STZ)-INDUCED DIABETIC RATS AND THEIR FETUSES. Albert D. Copeland, Jr.* and Susan P. Porterfield. Dept. of Physiology, Medical College of Georgia, Augusta, GA 30912.

Total serum amino acid levels are low in fetuses of diabetic women. It has been proposed that these depressed levels result from increased fetal tissue uptake and utilization. The present experiment was designed to determine the effect of STZ-induced diabetes in rats on placental transport and tissue uptake of the non-metabolizable amino acid α-amino-isobutyric acid (AIB). STZ was given to 3/4 of the rats (6.5 mg/100 BW ic) one week prior to mating. The remaining 25% served as intact controls (C). STZ-treated animals were divided into three groups; diabetic (D), diabetic treated with 4 IU/day Lente insulin sc (DI) and diabetic treated with 1 μg/100g BW/day T_4 days 1-17 of gestation and 2.5 μg/100g BW/day 3-5 dimethyl-3'-isopropyl-L-thyronine (DIMIT) days 18-21 (DTD). On day 22 of gestation, animals were injected 15 minutes prior to autopsy with .50 μCi/100g BW AIB sc. The tissues were solubilized for liquid scintillation counting. T_4 was measured by RIA. Although maternal serum DPM's were not different, fetal serum DPM's were lower in D and DTD groups than C. Net placental transport of AIB was less in D and DTD than C. Whole fetal tissue DPM's were greater in C than D and DTD. More AIB was taken up by fetal liver and fetal brain of C than of D and DTD. These data suggest that the low fetal serum amino acid levels reflect decreased net placental transport rather than increased fetal tissue amino acids uptake.

34.6

BINDING OF ANTISERA TO INSULIN AND S-100 PROTEIN IN MAMMALIAN RETINA AND OPTIC NERVE. Arup Das*, Ben Pansky*, G. Colin Budd and Carol R. Kollarits*. Medical College of Ohio, Toledo, OH 43699.

Mouse and human retina and optic nerve, fixed in glutaraldehyde, embedded in epoxy resin, and sectioned at 1.0 μm were treated with antisera against insulin and S-100 protein (a "marker" for glial cells). The sections were then stained using the peroxidase-antiperoxidase procedure. Insulin-like immunoreactivity was observed in the inner nuclear layer, outer and inner plexiform layers and in the ganglion cell layer of the retina. Glial elements, including Müller cells, were positively stained. Similar immunoreactivity was found in the glial cells of the optic nerves. Anti-S-100 protein immunoreactivity was found to stain identical components of both the retina and optic nerve. These new observations of an association between the distribution of S-100 protein and insulin or an insulin-like peptide and their possible significance are under further investigation. We acknowledge the expert technical assistance of J. Eric Uckele. This work was supported by grants from the Kroc Foundation and NIH Grant #AM33761.

34.7

DIETARY REGULATION OF ERYTHROCYTE INSULIN RECEPTOR INTERACTION AND ADIPOSE TISSUE PYRUVATE DEHYDROGENASE ENZYME ACTIVITY: METABOLIC EFFECTS OF DIETARY FIBER. J.O. Ogunwole*, E Knight*, J.S. Adkins, K.G. Thomaskutty*, and R.H. Pointer. Human Nutrition and Food, School of Human Ecology and Biochemistry Department, College of Medicine, Howard University, Washington, DC 20059

The aim of the present study was to examine the metabolic effects of high and low fiber intake in rats fed high and low protein diets. Male weanling Sprague Dawley rats were fed a high sucrose diet (AIN 75™ Recommendation) at different fiber levels for 4 and 8 weeks. The effect of these dietary treatments on erythrocyte insulin receptor interaction (IRI) and epididymal fat pad pyruvate dehydrogenase activity was measured by a standardized radioreceptor assay and PDH by the rate of oxidation of 1-^{14}C-pyruvate to $^{14}CO_2$. Fiber and protein intake significantly ($P < .01$) enhanced ^{125}I-insulin binding to rat erythrocytes as well as both basal and insulin stimulated activity of PDH. Scatchard analysis of the binding data shows increased receptor sites (Ro) ($P < .05$) and a relatively slower rate of changing affinity (as receptor occupancy $\frac{B}{Ro}$ = $Log_{\frac{B}{Ro}}$ increases) in fiber treated groups in a dose dependent manner. It appears that one of the beneficial effects of dietary fiber is increased tissue sensitivity to insulin and enhancement of the subsequent metabolic response to the cell membrane receptor signal.
(Supported by NSF grant PRM 8110709.)

34.8

LIVER MITOCHONDRIAL CITRULLINE SYNTHESIS (MCS): SHORT TERM EFFECTS OF SCHEDULED FEEDING IN RATS. Gale P. Beliveau* and Saul W. Brusilow, Dept. of Pediatrics, Johns Hopkins Univ., Baltimore,MD 21205

Although maximal rates of MCS are reported to be 40-50 nmol/min/mg protein, unexplained variability of MCS has been observed (Cohen et al.,JBC 257, 6896(1982)). We hypothesize that in vitro rates of MCS are a function of the fed state of the rat from which mitochondria are isolated. To test this hypothesis, rats were adapted to the feeding schedule of Potter et al. (Fed Proc. 27, 1238 (1968)). Rats had free access to food from 11pm to 7am every other evening; rooms were in darkness from 9pm to 7am every evening. Rates of MCS (nmol/min/mg protein) from NH_4Cl and ornithine were 32, 40, 29, 11, 7 and 2 at 2am (fed), 10am, 6pm, 2am,10am and 6pm, respectively. Rates of MCS from amino acids were also maximal during feeding, and were highest with glutamine followed by glutamate, glycine, aspartate and alanine. We conclude that the feeding state of the rat determines maximal rates of MCS which, in turn, may be a function of intramitochondrial enzyme levels or short-term regulatory factors. These data also explain the reported variability in MCS. (Supported by USPHS Grant HD 11134).

34.9

ANALYSIS OF INTESTINAL EPITHELIAL CELL ENERGY METABOLISM USING $^{14}CO_2$ AND ^{14}C-CITRATE ISOTOPE LABELING RATIOS. R.T. Mallet*, M.J. Jackson, and J.K. Kelleher*. George Washington Univ. Medical Center, Washington, D. C. 20037

Our objective is to determine the role of glutamine as a substrate for energy metabolism of the jejunal epithelium. Rat jejunal epithelial cells were incubated in buffered saline media containing either 5 mM glucose, 5 mM glutamine, 5 mM β-hydroxybutyrate, and 3 mM acetoacetate (A), 18 mM glutamine (B), or 18 mM mannitol (C). All media contained 1 μM succinate with ^{14}C labeling of either carbons 1 and 4 or carbons 2 and 3. The "CO_2 ratio", $^{14}CO_2$ production from [1,4-^{14}C] succinate divided by that from [2,3-^{14}C] succinate, was approximately 5 in media A and C. A CO_2 ratio greater than 1.0 indicates flux from the TCA cycle to products other than CO_2. In medium B the CO_2 ratio was approximately 14, indicating that glutamine increases the shunting of TCA cycle intermediates into nonoxidative pathways. The citrate labeling ratio, ^{14}C in carbons 4 + 5 of citrate divided by that of carbons 2 + 3, was measured for cells incubated in [2,3-^{14}C] succinate. In all media this ratio was approximately 0.05, indicating that flux of 4 carbon TCA cycle intermediates to citrate via acetyl CoA is not a major pathway. The principal non-CO_2 product of [2,3-^{14}C] succinate metabolism was alanine. Collectively, these results suggest that entry of glutamine carbon into the TCA cycle is coupled to alanine production from pyruvate derived from TCA cycle intermediates. (USPHS Support-GM22369)

34.10

RESPIRATORY QUOTIENTS, HEART RATE RESPONSE AND LACTATE PRODUCTION DURING EXERCISE IN ANOREXIA NERVOSA. Catherine E. Adams*, Ralph A. Nelson, John W. Erdman*, and Richard Boileau*. Carle Foundation Hospital and Univ. of Illinois, Urbana, IL 61801.

Exercise response was determined in 5 subjects with anorexia nervosa (AN) ages 18-26, body fat 8-21%. Data were compared with 3 normal subjects (C) ages 18-26, body fat 24-31%. All subjects walked for 1 hr on an inclined treadmill at 3 mph to achieve 50% VO_2 capacity. 50% maximal capacity was established by measuring heart rate (HR) during 2 pre-test periods. Expired air was collected during pre-test exercise test periods. Expired air and blood samples were collected before and at 10 min intervals during the 1 hr exercise test and post-exercise. Mean resting HR was 55 for AN and 61 for C. Mean HR response during exercise was 121 and 132 respectively.

		VO_2 ml/kg/min		RQ		Lactate		
	n	range	mean	range	mean	range at 40 &60 min	mean 40 min	mean 60 min
AN	5	17.5-24.5	20.3	.86-.91	.89	4.3-57.0	22.2	20.9
C	3	15.8-20.2	18.5	.81-.97	.87	7.5-12.3	9.2	12.0

No significant differences existed between anorexics and controls in amount of work performed or in rate of O_2 consumed during exercise when data are expressed on a per kg body weight basis. Despite resting bradycardia in AN, HR during exercise responds similarly in both groups. Lactate production was significantly greater at 40 and 60 min in AN which may indicate less efficient performance.

34.11

RECOVERY FROM ENERGY DEFICIT IN THE GOLDEN HAMSTER. K. T. Borer, E. R. Allen*, J. Stockton* Univ. of Michigan, Ann Arbor, MI 48109-2214, R. E. Smalley*, Emporia State University, Emporia, KS 66801, and L. Lundell*, Wheaton College, Norton, MA 02766

Hamsters lose weight if they are forced to feed at greater than 2-h intermeal intervals (IMIs) and recover from weight loses without increasing their food consumption if allowed to feed at 2-h IMIs (Borer et al Amer. J. Physiol. 236: E105-E112, 1979). Do changes in: general locomotion, extraction of metabolizable energy; heat production by the brown adipose tissue (BAT); insulin secretion; and activities of hepatic lipogenic enzymes, fatty acid synthetase (FAS) and malic enzyme (ME) account for the changes in the regulation of energy balance as a function of meal spacing and weight loss? Two hundred mature female hamsters were used. Increase in the IMI length (2-h to 5-h) blocked postprandial insulin release, reduced intermeal insulin concentration (18%) and reduced FAS (30%) and increased ME (61%) activities. Weight reduction (5-25%): suppressed the whole body oxygen consumption (VO_2) (0.05 ml O_2/g.h for each percent weight loss=PWL), general locomotor activity (75%), and plasma insulin concentration (50%); increased BAT VO_2 (4.6% for each PWL), FAS activity (25% for each PWL), and had no affect on other variables. We conclude that 1) reduced plasma insulin response and hepatic FAS activity contribute to, and increased ME activity counteracts, weight losses in infrequently feeding hamsters; and 2) reduced physical (but not BAT) and increased FAS activities contribute to more efficient nutrient utilization in frequently feeding underweight hamsters.

34.12

DEFICIENT COMPENSATIONS FOR THE ENERGY COST OF RUNNING IN GOLDEN HAMSTERS. R. J. Moffatt*, Western Washington Univ., Bellingham, WA 98225, K. T. Borer, A. C. Tsai*, Univ. of Michigan, Ann Arbor, MI 48109-2214, and R. Smalley*, Emporia State Univ., Emporia, KS 66801.

Since endurance exercise lowers body fat levels, we asked, Is energy balance adequately regulated during and after 4 weeks of voluntary running in female golden hamsters (n=58)? While daily and resting energy expenditures (VO_2) increased by 53.4% and 36.8%, respectively, during the first week of running, no compensatory processes were uncovered; brown adipose tissue heat production increased by 39.8% on day 10 of exercise, and consequently, body fat declined by 24.2%. By week four of exercise, increases in food intake (35.1%) and in activities of hepatic lipogenic enzymes fatty acid synthetase, FAS (105.7%) and malic enzyme, ME (114%) were compensating for, while the increased fecal energy loss (14.6%) was adding to, the energy cost of exercise (daily VO_2 was 25% above sedentary) and the body fat deficit (44.6%). Feeding (20.6% increase) and lipogenic (176.7% and 171.6% increases in FAS and ME activities, respectively) compensations continue to counteract, and fecal energy loss (11% higher than in sedentary) continues to add to the energy costs during week 1 of retirement; this reduces body fat deficit to 29.4% of sedentary level. By the fourth week of retirement, body fat content is normal, and no compensatory processes are operating except for the increased activity (81%) of the hepatic ME. Thus, the behavioral and physiological compensations for the energy cost of voluntary running in hamsters are quantitatively inadequate and initiated with a delay. The incurred body fat losses are therefore fully corrected only after the energy expenditure of running has ceased.

HYPERTENSION I

35.1

PLASMA CORTICOSTERONE (B) IN FETAL SPONTANEOUSLY HYPERTENSIVE RATS (SHR). Julie C. Breay*, Bernadette L. Plair*, and Margaret M. Mullins. Wright State University, Dayton, Ohio 45435

In SHR, elevated blood pressure and adrenocortical hyperplasia have been demonstrated as early as day 1 postnatally when compared to control Wistar-Kyoto (WKY) rats, suggesting prenatal hypertensive influences, possibly of adrenal cortical origin. This study looked at plasma B levels in dams and fetuses on gestation day 20 using a corticosteroid-binding globulin (CBG) competitive binding assay. Dams were sacrificed between 0800 and 1000 hrs, blood collected, and abdomen and uterus opened. Fetuses were sacrificed and blood collected in heparinized capillary tubes. Plasma from entire litters was pooled. Extraction was done first with petroleum ether to remove progesterone, then with ethanol. The ethanol extract was assayed using CBG solution containing ^{3}H-B. After incubation, samples were run on Sephadex G-25 columns and the bound fraction counted. Recovery was 89%. Fetal SHR had significantly higher B concentration than WKY (8.16 ± 0.93, n=7, vs. 5.48 ± 0.54 ng/dl, n=9, $p < .05$). Maternal plasma levels did not differ (SHR: 13.48 ± 5.05 vs. WKY: 10.87 ± 3.85 ng/dl, both n=3). These data suggest altered adrenal cortical function, specifically increased B production and/or secretion, prenatally that may contribute to later changes seen in SHR hypertension, including body fluid volume shifts at days 10 to 12 as reported previously by this laboratory. (Supported by Miami Valley Heart Chapter, American Heart Association.)

35.2

PRESSOR RESPONSES TO NOREPINEPHRINE IN 3-DAY RENAL ARTERY STENOSIS RABBITS WITH A DENERVATED KIDNEY. J. Alan Johnson, Debra G. Koivunen*, David W. Zeigler*, Wayne L. Fowler, Jr.*, and Charles G. Payne*. H.S Truman Mem. VA Hospital, and Depts. of Physiology and Surgery, Univ. of Missouri, Columbia, MO 65201

Two-kidney rabbits with unilateral renal artery stenosis (RAS) have enhanced pressor responses to vasoconstrictor substances, due to exaggerated contractions of the arterioles. RAS produces disturbances in the kidney that are sensed by receptors within the kidney, which then initiate a signal that leaves the kidney, by either a neuronal or a hormonal mechanism, to exert an effect on the arterioles. The present study was to determine if this signal is only neuronal. Six rabbits were subjected to RAS, and 6 rabbits were sham operated. Six additional rabbits were unilaterally renal denervated, and 6 other rabbits were renal denervated plus received RAS of the denervated kidney. Three days later, norepinephrine (NE) was infused i.v. into all rabbits at several doses, and the pressor responses were recorded. Rabbits with RAS, both renal innervated and denervated, had the same pressor responses to NE, which were substantially greater than the pressor responses to NE in the sham-operated controls and the renal denervated controls. Because renal denervation does not reduce the pressor hyperresponsiveness to NE in RAS rabbits, the signal from the kidney mediating pressor hyperresponsiveness is not transmitted by neuronal mechanisms. Thus, this signal from the RAS kidney probably is mediated by a hormonal factor.

35.3

CENTRAL β-ADRENOCEPTORS IN RENAL SYMPATHETIC NERVE ACTIVITY (RSNA) RESPONSE TO STRESS IN CONSCIOUS SPONTANEOUSLY HYPERTENSIVE RATS (SHR). J.P. Koepke* & G.F. DiBona. Dept. Int. Med., Univ. Ia. Col. Med. & VAMC, Iowa City, IA 52242.

In conscious SHR, the antinatriuretic response to stressful environmental stimulation is abolished by intracerebroventricular (icv) administration of β-adrenoceptor antagonists. We tested the hypothesis that icv β-adrenoceptor blockade (d,l-propranolol, timolol; 30μg in 2μl 0.9% saline) prevents the increased RSNA associated with stress in conscious SHR. The effects of stress on RSNA (integrated voltage) in SHR before and after icv saline vehicle, propranolol, and timolol are mean±SE integrator resets/min; *p < .05 vs. C; n=6 each.

	SALINE	SALINE	SALINE
Control	9.2 ± 2.7	10.6 ± 2.1	8.2 ± 0.9
Stress	14.8 ± 3.0*	17.8 ± 3.0*	13.4 ± 1.6*
Recovery	9.0 ± 2.0	10.5 ± 1.6	7.2 ± 1.0
	SALINE	PROPRANOLOL	TIMOLOL
Control	9.2 ± 2.5	8.1 ± 1.7	5.5 ± 1.0
Stress	14.5 ± 3.4*	8.7 ± 1.6	5.9 ± 1.3
Recovery	9.1 ± 2.3	7.6 ± 1.6	5.8 ± 1.1

ICV β-adrenoceptor blockade prevented the RSNA response to stress in conscious SHR. IV injection of the same drug doses had no effect on the RSNA response to stress. We conclude that CNS β-adrenoceptors mediate the increased RSNA resulting from stressful environmental stimulation in conscious SHR. (NIH AM 15843, HL 14388 and VA)

35.4

CHLORINE, CALCIUM, LIPID EFFECTS ON BLOOD LIPID PROFILES AND BLOOD PRESSURE. B. H. Douglas, P. T. McCauley*, R. J. Bull* and N. W. Revis*. Dept. Anatomy, Univ. Med. Ctr., Jackson, MS 39216-4505, Health Effects Research Lab., Cincinnati, OH 45268.

We have shown previously that decreased Ca and increased Cl intake raise plasma cholesterol (Physiologists 26:29, 1983). This study was designed to examine the effects of dietary Ca, Cl and fat on blood lipid profiles and blood pressure. Three groups of rats (10 each group) received 0, 1 or 10 ppm Cl in the drinking water plus 10% W/W lard in the diet and the minimum daily requirement (MDR) of Ca (0.5% Ca). Three additional groups received similar amounts of Cl and lard plus 80% MDR Ca (0.35% Ca). The control blood pressure of the 60 rats was 132 ± 5 mmHg (systolic). It rose by 6-12% in all the groups during the experimental period. The blood pressure elevation was not modified by the Ca or Cl intake. Cl and Ca affected the low density (LDL) and very low density (VLDL) lipoprotein fractions. In the rats on 100% MDR of Ca, the VLDL was 2 ± 1, 4 ± 1 and 6 ± 1 mg/dl respectively in the groups on 0, 1 and 10 ppm Cl. The VLDL was 16-72% higher than this in the rats on 80% MDR Ca. The LDL in the rats on 80% MDR Ca was 16-31% higher than the LDL in the rats on 100% MDR Ca. (This is a proposed presentation and does not reflect EPA policy).

35.5

HIGH DIETARY SODIUM INCREASES NET SODIUM AND POTASSIUM FLUXES IN LYMPHOCYTES FROM SPONTANEOUSLY HYPERTENSIVE (SHR) AND WISTAR KYOTO (WKY) RATS. P.B. Furspan, J.H. Myers, and D.F. Bohr. Univ. of Michigan, Ann Arbor, MI 48109

Experimental groups of 10 week old SHR and WKY were maintained on a high salt dietary regime (1.0% NaCl in the drinking water) for 7 weeks. Control groups of SHR and WKY received regular tap water. Lymphocyte Na and K contents and net fluxes at 4°C, plasma Na and K, and systolic blood pressure were measured at the end of the experimental period. Lymphocyte Na and K contents, plasma Na and K, and systolic blood pressure were not changed by the experimental treatment. Na and K fluxes, however, were altered.

	WKY		SHR	
	Control	High Salt	Control	High Salt
Na Flux	3.96 ± 0.8	6.75 ± 1.1	4.92 ± 0.1	9.76* ± 1.0
K Flux	4.3 ± 0.5	7.89* ± 0.9	7.10 ± 0.9	7.83 ± 1.7

N = 4 for all values. *p <0.01, t-test.

The high Na diet increased sodium flux in the lymphocytes of the SHR group and produced membrane characteristics in the lymphocytes of the WKY rats which were similar to those of the SHR.(Supported by NIH grants HL 18575 and HL 27020)

35.6

EXTRACELLULAR CALCIUM (Ca) AND NA^+/K^+ REGULATION IN SHR CULTURED VASCULAR SMOOTH MUSCLE CELLS (VSMC). H.Tamura*, L.Hopp*, A.Tokushige*, M.Kino*, and A. Aviv. NJ Med. School, Hypertension Research Unit, Newark, NJ 07103

To delineate the influence of Ca on Na^+ and K^+ homeostasis in serially passed cultured VSMC, cells derived from SHR, Wistar Kyoto (WKY), and Wistar (W) rats were subjected to Ca-deficient (Ca-D) medium and changes in intracellular Na^+ (Na^+i) levels and $^{86}Rb^+$ and $^{22}Na^+$ fluxes were examined. Ca removal resulted in substantial increase in passive Na^+ and Rb^+ (K^+) movement associated with augmented Na^+-pump activity, (69% increase in the pump activity for SHR, 42% for WKY, and 36% for W). In Ca-D medium, steady state Na^+_i levels (mEq/l;Mean±SEM) were significantly higher ($p<.001$) than those of basal values (Ca=2mM) in all three groups (15.84±.68 vs. 6.03±.20 for SHR, 9.89±.64 vs. 5.46±.26 for WKY, 10.44±.64 vs. 5.91±.16 for W, n=36), SHR being the highest. The Na^+-pump activity (ouabain-sensitive Rb^+ influx rate constant; expressed per min) was stratified according to the Na^+_i concentrations: .74±.03 for SHR, .56±.02 for WKY, .62±.03 for W, n=36-40. We conclude that Ca plays an important role in cellular Na^+/K^+ regulation and that the Na^+_i of SHR VSMC is more sensitive to Ca removal than normotensive controls.

35.7

MELITTIN EFFECT ON NA^+/K^+ REGULATION IN CULTURED SHR SKIN FIBROBLASTS (SF). M.Kino*, A.Tokushige*, L.Hopp*, H.Tamura*, and A.Aviv. NJ Med. School, Hypertension Research Unit,Newark, NJ 07103

We have examined the effect of melittin on Na^+/K^+ regulation in cultured SF of the SHR, Wistar Kyoto (WKY) and Wistar (W) rats. The effect of melittin in all groups was maximal within 10 min incubation at 2mM calcium medium. Associated with this effect, we showed augmented activity of the Na^+-pump. Melittin dose response experiments (table,mean ± SEM, number of observations indicated in brackets) showed that at a concentration of 1600ng/10^6 cells, SHR SF exhibited the highest intracellular Na^+ (10^{-8}Eq/10^6 cells), and the lowest intracellular K^+ among the three groups.

		Melittin (ng/10^6 cells) 400	800	1600
Na^+	SHR	3.2±.1(12)**	14.2±.4(11)**	25.1±1.7(12)**,++
	WKY	3.8±.2(7)	14.9±.5(12)	20.4± .6(12)
	W	2.0±.1(11)	10.6±.3(9)	17.4±1.0(12)
K^+	SHR	22.2±.4(12)**	14.1±.7(12)**	5.8± .3(12)**,++
	WKY	23.5±.7(7)	15.3±.5(12)	8.5± .4(12)
	W	25.9±.9(12)	16.8±.4(12)	7.6± .2(12)

** p<.01 for SHR vs W ++ p<.01 for SHR vs WKY

These findings underscore the relatively greater sensitivity of SHR SF as compared to WKY and W cells to melittin. Thus, melittin can be utilized to probe abnormalities in cellular Na^+/K^+ regulation of the SHR.

35.8

REDUCED MEMBRANE POTENTIAL IN VASCULAR SMOOTH MUSCLE CELLS OF RATS WITH EARLY AND CHRONIC ONE-KIDNEY, ONE-CLIP HYPERTENSION. Richard L. Shoemaker and Henry W. Overbeck. Depts. of Physiol. and Biophysics, and Medicine, Univ. of Ala. in Birmingham, Birmingham, AL 35294.

Intracellular membrane potentials (Em's) were measured in vitro in VSM of the caudal artery from one-kidney (1K, normotensive), and one-kidney one-clip (1K1C, hypertensive) male Sprague-Dawley rats. Cells were punctured from the adventitial side with 3M KCl filled microelectrodes, tip resistance of 40 to 70 MΩ, and the effect of ouabain (1mM) or $\Delta[K^+]_o$ was observed. The suffusion fluid (physiol. salt solution) was maintained at 36°C, and oxygenated with 95% O_2-5%CO_2. In chronic 1K1C rats (4-6wks. of systolic pressure>140mmHg) the Em's were -51.1±01.7mV. compared to -46±1.1 for 1K controls ($P<0.01$, no. of punctures/no. of animals =170/14). The ΔEm due to ouabain (1mm) was less in the 1K1C (+6.3mV) compared to 1K (+10.1) ($P<0.01$, n/a=23/11); the Em's of the two groups after ouabain were the same. The ΔEm after 10mM $[K^+]_o$ (following the inhibition of the Na-K pump with $[K^+]_o$) was greater in the 1K (+15.1mV) compared to 1K1C (+13.1), $P<0.05$, n/a=38/6. In early hypertension the same qualitative results were obtained but the magnitude of the differences were less. The cell membrane resistance increased as the $[K^+]_o$ decreased; the resistance of the VSM cell membranes were similar in 1K and 1K1C rats. These results suggest reduction in Na-K pump activity but do not exclude changes in membrane ion permeability.

36.1

EFFECT OF BRACHIAL PLEXUS BLOCK ON THE RESPONSE OF FOREARM BLOOD FLOW TO LOCAL TEMPERATURE. C.B. Wenger, L.A. Stephenson, and M.A. Durkin*. John B. Pierce Fdn. and Yale Univ. Sch. of Med., New Haven, CT 06519.

Cooling superficial blood vessels of experimental animals potentiates constrictor responses to agonists or electrical stimulation, but has little effect on unstimulated vessels. This study was done to test whether the effect of local temperature on human forearm blood flow (FBF) also depends on interaction between temperature and agonist. Six subjects sat with one arm suspended at shoulder level and enclosed in a plastic bag through which blew an air stream, whose temperature was controlled so as to regulate forearm skin temperature (T_{sk}). We lowered T_{sk} to 25°C, and after 20 min measured FBF every 30 s for 10 min, with Whitney strain gauges. We then raised T_{sk} by 2.5°C steps to 40°C, and measured FBF for at least 10 min at each step. In control experiments, subjects were lightly clad in an ambient temperature of 27-29°C, adjusted to minimize the subject's overall thermal sensation. Experiments were repeated after brachial plexus block (BPB), induced by injecting 40 ml of 0.25% bupivicaine without epinephrine into the axillary sheath. Mean FBF rose from 1.1 ml/(100 ml·min) at T_{sk} of 25°C to 13.7 ml/(100 ml·min) at 40 °C in control experiments, and from 3.4 ml/(100 ml·min) to 14.8 ml/(100 ml·min) after BPB. The difference was significant ($P < 0.05$) only at T_{sk} of 25 and 27.5°C. The effect of T_{sk} on FBF is largely independent of neural activity, since it is unaffected by neuronal blockade.

36.2

MECHANISM OF ACTION OF DOPAMINE ON PERIPHERAL CIRCULATION DURING LOCAL COLD EXPOSURE. Carl A. Ohata. U.S. Army Research Institute of Environmental Medicine, Natick, MA 01760

Dopamine produces a dose-dependent vasodilation and hyperemia in the femoral artery and warming and heat dissipation in the footpad of the locally cold exposed cat hindlimb, as well as pressor responses and a bradycardia which is oftentimes interrupted by a momentary tachycardia. This study examined the mechanisms in which dopamine produced these effects. Mean femoral arterial resistance and blood flow, footpad temperature and heat loss, mean arterial pressure, and heart rate were simultaneously monitored in cats anesthetized with α-chloralose (50 mg/kg). The experimental procedure involved testing the effects of intravenous bolus infusions of 1, 10 and 100 μg/kg dopamine during hindlimb exposure to room air (22°C), cold (0°C), and after pretreatment with various blocking agents. All responses to dopamine persisted after pretreatment with ergonovine and propranolol suggesting that the responses were not mediated by dopamine receptors or β-adrenergic receptors. The bradycardia induced by dopamine was blocked by atropine and bilateral cervical vagotomy suggesting mediation by vagal cholinergic mechanisms. The pressor response, peripheral hyperemia and tachycardia spike were blocked by phentolamine suggesting mediation by α-adrenergic receptors. It is uncertain whether the peripheral hyperemia was mediated by baroreceptor reflex inhibition of descending sympathetic vasoconstrictor tone during dopamine-induced pressor responses or by dopamine-induced ganglionic inhibition of descending sympathetic vasoconstrictor tone.

36.3

COMPARISON OF ATP VS ADENINE NUCLEOTIDES ON PORTAL AND HEPATIC ARTERIAL FLOWS IN THE PERFUSED RAT LIVER
Joong-Woo Lee* and James P. Filkins. Department of Physiology, Loyola University of Chicago, Stritch School of Medicine, Maywood, IL. 60153

We have previously reported that ATP decreases portal perfusion flow in the isolated perfused rat liver (*Fed. Proc. 43*: 1027, 1984). The current study investigated the site of ATP action, the effect of ATP on hepatic portal and arterial flows and a comparison of various adenine nucleotides and adenosine on perfusion flows. Changes in liver weight were measured by a force transducer (Grass FT03C). Hepatic arterial perfusion pressure alterations under constant perfusion flow were determined by a Statham pressure transducer (P23DC). ATP at 10, 40 and 160 μM decreased liver weight (gm) from a control value of 12.5±0.50 to 11.9±0.52, 11.0±0.48 and 10.2±0.41 respectively. ATP increased hepatic arterial perfusion pressure from 77.1± 2.4 to 96.8±4.5 and 150.4±9.6 mmHg at 5 and 25 μmoles injection respectively. The adenine derivatives including adenosine, AMP, ADP and ATP all decreased perfusion flow in following order: ATP > ADP > AMP = adenosine. These studies indicate (1) ATP acts on both portal vein and hepatic arterial systems, (2) perfusion flow decreases are due to increasing resistance of inlet hepatic sphincters and (3) while all adenine derivatives decrease perfusion flow, ATP is the most potent.
(Supported by a grant from E. M. Bane Charitable Trust Fund.)

36.4

SELECTIVE PROSTAGLANDIN SYNTHESIS INHIBITORS AND JEJUNAL CAPILLARY FILTRATION COEFFICIENT (CFC) DURING ABSORPTION.
M.J. Mangino* and C.C. Chou. Departments of Physiology and Medicine, Michigan State University, East Lansing, MI 48824.

Three series of experiments were performed in anesthetized dogs to study the effects of luminal placement of digested food, mefenamic acid (M), and imidazole (I) on jejunal CFC. In the first series (N=14), luminal placement of digested food caused a significant increase in jejunal CFC throughout the 16 min placement period. Before food, CFC($ml \cdot min^{-1} \cdot mmHg^{-1} \cdot 100g^{-1}$) was .353 ± .02 and during four 4 min placement periods, food increased CFC to .472 ± .04, .476 ± .03, .431 ± .02, and .527 ± .02, respectively. In series II (N=6), the effect of I (thromboxane synthetase inhibitor) was examined. Imidazole per se significantly increased CFC, but had no effect on the food-induced increase in CFC during the first 8 min of food placement. Imidazole, however, significantly enhanced the food-induced increase in CFC during the last 8 min of food placement. In series III (N=6), the effect of M (cycloxygenase inhibitor) was examined. M per se had no effect on CFC and did not affect the food-induced increase in CFC at any time during the 16 min food placement period. Conclusions: food that contains equal amounts of fat, protein, and carbohydrates in the jejunal lumen increases jejunal CFC. Total prostaglandin synthesis inhibition has no effect but selective inhibition of thromboxane synthesis enhances jejunal CFC before and during food placement.
(Supported by NIH Grant HL-15231.)

36.5

MICROSPHERE PASSAGE THROUGH THE INTESTINAL CIRCULATION: VIA SHUNTS OR CAPILLARIES? L.C. Maxwell, A.P. Shepherd and C.A. McMahan*, Depts. of Physiology and Pathology, Univ. of Texas Health Science Ctr., San Antonio, TX 78284.

Significant quantities of 9μm spheres are not trapped in the intestine following intra-cardiac or intra-arterial injection. Nine μm spheres could possibly reach venous blood through non-capillary (shunt) vessels, or because the frequency distributions of capillary and sphere diameters overlap, spheres could simply pass through capillaries. Therefore, we developed probabilistic models to predict the size and percentage of spheres that should reach venous blood. The model assumes that sphere delivery is independent of sphere diameter and that spheres pass through capillaries of equal or larger diameter. The model predicts the percent passage in the range we observed in canine intestinal circulation. We conclude that the passage of spheres (mean 9μm, S.D. = 1) through intestinal capillaries (mean 7.38μm, S.D. = 1.4) adequately accounts for spheres in venous blood. We also injected a mixture of spheres ranging in diameter from 5 to 20μm. The predicted frequency distribution for microsphere diameters in venous blood agreed with the observed data. Also, with the wider range of sphere diameters, the filtering effect of passage through the intestinal circulation was readily demonstrated. The filtering effect may be used to estimate the frequency distribution of capillary diameters. (Supported by American Heart Association).

36.6

MEASUREMENT OF MICROCIRCULATORY BLOOD FLOW BY DIFFERENTIAL LASER-DOPPLER SPECTROSCOPY IN THE RAT GRACILIS MUSCLE AND KIDNEY. R.J. Roman, C.A. Smits*, and J.H. Lombard. Dept. of Physiology; Med. Coll. Wisconsin; Milwaukee, WI 53226

We evaluated a Periflux dual channel differential laser-Doppler flow meter (Perimed Corp.; Stockholm, Sweden) for measurement of microcirculatory blood flow in the gracilis muscle, renal cortex, and renal papilla of the rat. In 8 rats, the left gracilis muscle was exposed. Total gracilis blood flow was measured with an electromagnetic flow probe on the femoral artery after tying off branches not perfusing the muscle. Perfusion pressure was varied by occluding the lower aorta. Microvascular blood flow measured with the laser-Doppler flow meter (LDF) was highly correlated to total gracilis blood flow (TBF) in ml/min. LDF=11.5 TBF + 7.4, r=.84. Likewise in 10 rats, tissue blood flow measured by LDF in the renal cortex was highly correlated to total renal blood flow measured with an electromagnetic flow probe on the renal artery. LDF=10.3 RBF + 10.4, r=.78. In the exposed papilla of 21 rats, LDF was highly correlated to papillary blood flow estimated by ^{51}Cr-labelled red cell accumulation (RCF). LDF=6.7 RCF + 11.4, r=0.83. These results indicate that blood flow in small regions (<0.5 mm^3) of a variety of microcirculatory beds can be quantitated using laser-Doppler spectroscopy. (Supported by NIH #P01 29587).

36.7

CORONARY ARTERIAL DISTRIBUTION AND COLLATERAL VESSELS IN CANINE, PORCINE, AND EQUINE (PONY) HEARTS: ANIMAL MODELS FOR RESEARCH IN HUMAN CORONARY ARTERY DISEASE. Lisa A. Dawson * and James F. Amend. University of Nebraska-Lincoln, Lincoln, NE 68583 - 0905

Two primary animal models for research in coronary arterial structure and function have, historically, been dog and pig. Recent studies have suggested, however, that equine heart may be a third option. We studied gross and sub-gross patterns of primary and collateral vessel distribution in each of these species. Hearts were obtained following experimental surgical studies conducted under general anesthesia. Each heart was perfused with Microfil latex rubber solution via the root of the left coronary artery. Hearts were cooled until injectate was cured. Photographs of gross surface vessel distribution were made, after which each heart was transversely sectioned, and the slices cleared in increasing concentrations of glycerine. Results confirmed that arterial distribution is left predominant in dog heart, but right predominant in hearts of pig and pony. Dog hearts showed primarily subepicardial collateral vessels. Pig hearts showed few collateral vessels, but dense capillary beds. Pony hearts presented evidence of subendocardial collaterals, in considerably greater abundance than dog or pig hearts. These results suggest that the pony heart should be further examined in terms of collateral vessel formation after induced chronic ischemia. (This study was supported by the Research Council, University of Nebraska-Lincoln, and by the Agricultural Research Division, IANR.)

36.8

EFFECTS OF 100 PERCENT OXYGEN EXPOSURE ON THE CARDIOVASCULAR RESPONSES TO VASOACTIVE HORMONES. Jeffrey C. Sventek* and Edward J. Zambraski. Rutgers Univ., New Brunswick, NJ 08903

A comparison of the systemic response to exogenously administered vasoactive hormones was made in two groups of anesthesized dogs; one group ventilated with ambient air (20% O_2) (N=4), and another group ventilated with 100% oxygen (N=7). Bolus injections (i.v.) of angiotensin I (AI), angiotensin II(AII), and prostaglandin E_2(PGE_2) were given before and during 8 hours of exposure. Arterial injections of PGE_2, sodium nitroprusside (NP), and phenylephrine(PE) were also made. Listed in the table are changes in mean arterial pressure (MAP)(mmHg) before and after 4 and 8 hours of treatment. Values are mean ± SEM (*p<0.05 vs. control).

		Pre-exposure Control	Four hours Post exposure	Eight hours Post exposure
AI	Normoxic	18.7±1.2	20.0±3.6	23.3±3.5
	Hyperoxic	18.6±2.5	27.1±2.6*	26.3±2.2*
AII	Normoxic	24.0±1.7	24.0±2.6	30.7±3.8
	Hyperoxic	23.4±2.3	32.9±2.4*	33.4±1.9*

Basal MAP and heart rate were not altered by 20% or 100% oxygen. Vasoactive responses to PGE_2(i.v. and i.a.), NP, and PE were unaltered by 8 hours of 100% oxygen. Vasoconstrictor responses to AI and AII, however, were significantly enhanced.

36.9

ASCENDING AORTIC IMPEDANCE PATTERNS IN THE KANGAROO. Wilmer W. Nichols, Albert P. Avolio*, and Michael F. O'Rourke*. Univ. of Florida, Gainesville, FL 32610 and Univ. of New South Wales, Sydney, Australia

Pulsatile pressure and blood flow velocity were measured and input impedance calculated in the ascending aorta of 15 rock kangaroos. The pressure wave displayed a very large secondary wave that began in late systole or early diastole and continued throughout most of diastole. The peak of this secondary wave (which almost always occurred in diastole) was often greater than peak systolic pressure. The impedance spectral patterns obtained in the ascending aorta showed large amplitude fluctuations and were similar to those measured in a uniform transmission line or a rubber tube with a closed end. The large secondary wave in the aortic pressure record results from apparently intense wave reflection from peripheral vascular beds. This contention is supported by the configuration of the impedance spectral pattern which is explained on the basis of a single functionally discrete reflecting site in the lower part of the body. These findings are explicable on the basis of body size and shape and the extreme eccentric location of the heart within the body. Wave reflection from the diminutive upper body are so small that they are totally dominated by intensive wave reflection from the large and muscular lower body.

PULMONARY GAS EXCHANGE, PULMONARY VENTILATION AND DIFFUSION OF GASES

37.1

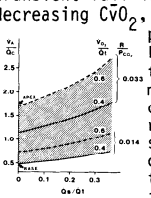
MECHANISMS OF ALVEOLAR-ARTERIAL PO2 DIFFERENCES DURING EXERCISE IN MAN. **M. Hammond*, G. Gale*, K. Kapitan*, A. Ries*, P. Wagner. Dept. Med., UCSD, La Jolla, CA. 92093**

Heavy exercise in athletes may result in mild arterial hypoxemia even at sea level. To examine the mechanism of this hypoxemia volunteers exercised at several workloads (resultant $\dot{V}_{O2}$ 20-60 ml·(kg·min)$^{-1}$) and $\dot{V}_E$, cardiac output, $\dot{V}_{O2}$, $\dot{V}_{CO2}$, pHa, P_{O2}, P_{CO2}, blood temperature and $\dot{V}_A/\dot{Q}$ distribution (multiple inert gas elimination) were measured simultaneously under steady state conditions. Three of four subjects who developed hypoxemia showed a linear increase in A-a D_{O2} versus $\dot{V}_{O2}$ of 7.27±1.44 torr·(L/min)$^{-1}$ (r= 0.813). A fourth subject showed no hypoxemia. Two who developed hypoxemia showed increased $\dot{V}_A/\dot{Q}$ inequality: logSDQ (log standard deviation of blood flow) from 0.50 at rest to 0.95 at 60ml·(kg·min)$^{-1}$ $\dot{V}_{O2}$ and logSDQ from 0.58 at rest to 1.4 at 57ml·(kg·min)$^{-1}$ $\dot{V}_{O2}$ respectively. 100% oxygen at high $\dot{V}_{O2}$ and cardiac output improved the $\dot{V}_A/\dot{Q}$ distribution in these subjects. In the third case hypoxemia could not be explained on the basis of $\dot{V}_A/\dot{Q}$ inequality thus suggesting diffusion limitation as the mechanism. These preliminary results suggest that hypoxemia and the development of $\dot{V}_A/\dot{Q}$ inequality or diffusion limitation is variable, and likely depends upon interaction between cardiac output, pulmonary vascular tone, pulmonary capillary volume, and mixed venous P_{O2}. (Supported by HL#17731 and the British Columbia Health Care Research Foundation.)

37.2

EFFECTS OF ATELECTASIS ON PULMONARY GAS EXCHANGE: THEORY. Julio C. Cruz. Medical College of Ohio, Toledo, Ohio 43699.

Rahn's equation $\dot{V}A/\dot{Q}t=864R(CaO_2-C\bar{v}O_2)/PACO_2$(AJP 158:21,1949) was obtained from the Fick and alveolar ventilation ($\dot{V}A$) equations.Since the anatomical shunt($\dot{Q}s$)was not considered in that model,$\dot{Q}t=\dot{Q}c$.In order to analyze the influence of atelectasis (a shunt-like effect)on gas exchange, the modified shunt equation (Cruz,Fed Proc, 41:1129,1982) was combined with the above equation yielding $\dot{V}O_2/\dot{Q}t=[(1-\dot{Q}s/\dot{Q}t)/864][PACO_2/R][\dot{V}A/\dot{Q}c]$.When atelectasis develops ($\dot{Q}s/\dot{Q}t>0$)a transient fall in O_2 uptake ($\dot{V}O_2$) follows which, if associated with a proportionally reduced CO_2 output ($\dot{V}CO_2$), leaves R unaltered. If Qt does not change,$\dot{Q}c$ will be reduced by $\dot{Q}s(\dot{Q}c=\dot{Q}t-\dot{Q}s)$,hence an increase in $\dot{V}A/\dot{Q}c$ is expected. On the other hand, since $\dot{V}O_2$ falls without altering R, $\dot{V}A$ must fall in order to keep $PACO_2$ constant,leaving $\dot{V}A/\dot{Q}c$ unaltered. Assuming a constant O_2 consumption, the transient fall in O_2 uptake is restored (new steady state) by decreasing $C\bar{v}O_2$, resulting in a constant $\dot{V}O_2/\dot{Q}t$. In clinical practice, as the shunt varies with augmenting F_IO_2, $\dot{V}O_2/\dot{Q}t$ does not remain constant and $C\bar{v}O_2$ tends to rise (Anesthesiology, 57:A122, 1982) making atelectasis unlikely. Rearranging the derived equation shown above the $\dot{V}A/\dot{Q}c$:$\dot{Q}s/\dot{Q}t$ relationship can be studied (Figure). As the shunt increases, $\dot{V}A/\dot{Q}c$ also increases in a curvilinear manner.Furthermore, the $\dot{V}A/\dot{Q}c$ distribution (stippled area) widens as the shunt increases, and it shifts to high $\dot{V}A/\dot{Q}c$ values.



37.3

INTERACTION OF HIGHLY SOLUBLE INERT GASES WITH AIRWAY MUCOSA DURING EXHALATION. M.P. Hlastala, M. Middaugh* and D.D. Ralph*, University of Washington, Seattle, WA 98195.

The interaction of soluble gases with the airway mucosa during exhalation was studied by measuring the profile of partial pressure vs exhaled volume (PPP) for ethyl alcohol (EtOH). The Ostwald partition coefficient (λ) for EtOH at 37°C in blood and water is approximately 1750 and 2130, respectively. The alveolar EtOH concentration is uniform among alveoli with differing ventilation-perfusion ($\dot{V}_A/\dot{Q}$) ratio because λ for EtOH is much higher than the range of $\dot{V}_A/\dot{Q}$ ratio in the normal lung. Therefore, the alveolar plateau (Phase III) of the PPP would be expected to be flat. The PPP of normal human subject volunteers was recorded using a Balzers quadrupole mass spectrometer (MS) after ingesting EtOH. Blood EtOH partial pressure was measured with the MS after extraction in air. Inspired air temperature was varied between -10°C and +45°C. The experimentally measured PPP was always positively sloped with end-tidal P_{EtOH} exceeding blood P_{EtOH}, by as much as 60%. The difference between end-tidal and blood P_{EtOH} increased after warm air inspiration and decreased after cold inspiration. These findings can be explained by the simultaneous exchange of heat and EtOH between the exhaled gas and the airway tissue. A simple mathematical model of the trachea including simultaneous heat and mass exchange was developed which adequately simulates the experimental observations. (supported by NIH grants HL12174, HL24163 and HL00891)

37.4

HEAT AND WATER EXCHANGE IN AN AIRWAY TISSUE MODEL. R.J. Gard*, M.P. Hlastala and A.L. Babb*, University of Washington, Seattle, WA 98195

The dynamics of heat and mass transport in air passing through an idealized dog trachea surrounded by tissue have been simulated. The time-dependent concentration profiles for each region were determined using an alternating direction, implicit numerical method. The movement of isopleths and the change of cross-sectional profiles for temperature, water-vapor concentration, and relative humidity (RH) in the airway have been plotted at various time steps during the full respiratory cycle. For a 22 cm trachea, an inspired air temperature of 27°C, an RH of 50%, and an average flow rate of 250 ml/sec, tissue-air interface temperatures at 2.2, 11.0 and 22.0 cm from the inlet will decrease by 1.4, .8, and .5°C, respectively. The centerline water-vapor concentration is 75% of the saturated value at 37°C and is not supersaturated at any time during the inspiration. Changing the inspiration temperature to 7°C decreases the interface temperatures 4.0, 1.8, and 1.4°C, respectively. A significant amount of cooling of airway mucosa takes place while breathing cool air. With a low inspired temperature of 7°C, supersaturation occurred for much of the time within the trachea because the rate of flux of water is slightly greater than the rate of flux of heat. The model can be used to predict the envelope of inspiration temperature and RH such that supersaturation does not occur. (supported by NIH grants HL12174 and HL24163)

37.5

ELECTRICAL VERSUS MECHANICAL DUTY CYCLES IN HIGH-FREQUENCY JET-VENTILATION. Howard J. Bryant and Peter H. Abbrecht. Departments of Physiology and Internal Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD 20814

The design of a system for high-frequency jet-ventilation is described. Mongrel dogs were anesthetized with an initial injection of pentobarbital (25 mg/kg) supplemented by a constant infusion of 100 mg/hr through a femoral vein. Jets of 10-40 psi humidified air were introduced into the trachea through an eight gauge needle inserted through the cricothyroid membrane. Gas flow to the needle was interrupted by a solenoid valve operated by a controller circuit. The controller allowed the independent setting of duty cycle (ratio of inspiratory time to total cycle time) from 10-50% and respiratory frequency from 10-350/min. When duty cycles were set using the electrical control signal to the solenoid, delivered gas volumes were up to 89% greater than volumes calculated from continuous flows. These errors were caused by unequal time delays for solenoid opening and closing. There was a 11.3 ms delay between the electrical activating signal and the beginning of air flow to the dog. Upon solenoid closure there was a 39.7 ms delay between the electrical signal and the termination of air flow. This 28.4 ms difference between these delays produced errors in flow that increased with increasing frequency and with decreasing duty cycle. The controller described here compensates for this difference in delay and delivers volumes within 3.4% of those calculated from continuous flows. (Supported by USUHS Grant RO7659)

37.6

DETERMINANTS OF RESPIRATORY GAS EXCHANGE DURING HIGH-FREQUENCY JET-VENTILATION. Peter H. Abbrecht and Howard J. Bryant. Departments of Physiology and Internal Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD 20814

The effectiveness of high-frequency ventilation is a function of gas delivery pressure (D.P.), duty cycle (insufflation time/total cycle time; D.C.) and respiratory frequency (F). Ten dogs, anesthetized with sodium pentobarbital, were ventilated with a standard cricothyrotomy needle using a controller that allowed separate setting of D.P., D.C. and F. Arterial PO_2 and PCO_2 were measured after achieving steady state gas exchange at 15-20 different combinations of D.P., D.C., and F in each dog. There was a slight increase in $PaCO_2$ and larger decreases in PaO_2 as frequency was increased from 10 to 350 breaths per minute. Increasing D.P. and D.C. resulted in reduction in $PaCO_2$ and increases in PaO_2. The changes in alveolar ventilation corresponding to the blood gas changes resulted from the interaction of dead space ventilation and upper airway leakage occurring during breaths of different duration. Decreases in leakage during short breaths tended to compensate for the increased fractioned dead space ventilation at high frequency, thus minimizing effects of frequency on gas exchange. The results may be explained using a mathematical model based on standard pulmonary mechanical formulations. (Supported by a grant from the U.S. Army Medical Research and Development Command and USUHS Grant RO7659)

37.7

INFLUENCE OF POSTURE ON THE DISTRIBUTION OF INSPIRED GAS DURING TIDAL BREATHING. **Ken-ichi Arita*, Steven M. Lewis and Charles Mittman, Dept. of Biomedical Engineering U. So. Cal., L.A. Ca 90089, City of Hope, Duarte Ca 91010.**

The washout of an insoluble tracer from the lung may be fit to with two or more compartments representing poorer and better ventilated lung regions (PVR and WVR respectively). We have shown that using boli of a second insoluble gas given at a fixed point during selected inspirations of a multibreath washout test, the proportions of labeled inspired ventilation reaching PVRs and WVRs may be determined. Using boli delivered at several points during inspiration allows quantification of the distribution of inspired ventilation to well and poorly ventilated lung units. We studied six normal subjects breathing through large bore solenoids controlled to maintain tidal volume at 600cc. Boli consisting of 15cc of 80% He,20% oxygen were delivered over 75 msec labeling approximately 125cc of inspired gas. Boli were delivered after 50 cc had been inspired to make early inspiration (EIB) and after 300 cc had been inspired marking mid inspiration (MIB). Subjects were studied in the seated upright and the supine positions. In both the upright and the supine positions, significantly more of EIB went to the PVRs than MIB. In the supine position the fraction of the MIB reaching the PVRs was significantly lower than in the upright position. Differences in the distribution of the EIB were non significant. This work supported by HL 30711.

37.8

TEMPERATURE DEPENDENCE OF BINARY WATER VAPOR DIFFUSIVITY IN AIR. C. V. Paganelli and P. R. Sotherland*, State Univ. of N.Y. at Buffalo, Buffalo, NY 14214.

Studies of rates of water evaporation from the surface of skin, bird eggs, and plant leaves require knowledge of the diffusion coefficient of water vapor in air ($D_{H2O,air}$) at different temperatures if the role of diffusive conductance across the boundary layer is to be evaluated. Surprisingly few data are available for $D_{H2O,air}$ as a function of temperature in the range of biological interest. Accordingly, we determined $D_{H2O,air}$ at 8 different temperatures over the range 10 - 45°C using a modification of the method of Schwertz and Brow (*J. Chem. Phys.* 19: 640-646, 1951). The value of $D_{H2O,air}$ in $cm^2\ s^{-1}$ rose from 0.227 ± .004 (SE) at 10°C to 0.273 ± .002 (SE) at 45°C. The temperature dependence of the diffusion process at 1 atmosphere may be expressed as $D_{H2O,air} = .000035\ T^{1.55}$, where T is absolute temperature. Our value for the exponent of T is in good agreement with the theoretical value of 1.50 and Schwertz and Brow's experimental figure of 1.54.

(Supported in part by NIH Grant #P01 HL 28542.)

37.9

HEAT TRANSFER FROM BIRD EGGS: HOW IMPORTANT IS THE BOUNDARY LAYER? P. R. Sotherland*, H. Rahn, and C. V. Paganelli. Dept. Physiol., State Univ. of New York at Buffalo, Buffalo, NY 14214

Heat is transferred from the avian embryo to its surroundings through several thermal resistances arranged in series: thermal resistance of the perfused embryonic tissues, the shell itself, the shell membranes, and finally the air boundary layer at the outer surface of the shell. We investigated the relative importance of these resistances by measuring temperatures at the locations listed below in chicken eggs containing 17 - 19 d embryos while their metabolic rate was measured in an open circuit chamber submerged in a constant-temperature water bath. The results shown below support the contention that the boundary layer surrounding these eggs provides the major resistance to heat loss. In this regard heat loss differs from water loss in which the boundary layer offers relatively minor resistance to diffusion of water vapor from the interior of the egg to its surroundings (Tracy and Sotherland, *Physiol. Zool.* 52: 63-66; Spotila et al., *Physiol. Zool.* 54: 195-202, 1981).

	Temperature (C)	ΔC	Fraction of Total ΔC
Embryo	39.5		
Between shell and membranes	39.3	0.2	.12
Outer surface of shell	39.2	0.1	.06
Air	38.1	1.2	.82

(Supported by NIH Grant #PO1-HL 28542)

EXERCISE AND WEIGHTLESSNESS

38.1

MUSCLE PERFORMANCE AND METABOLISM IN MAXIMAL ISOKINETIC CYCLING AT SLOW AND FAST SPEEDS. N. McCartney*, N.L.Jones, G.J.Heigenhauser, T. Graham, L. Spriet, J. Kowalchuk and J.R. Sutton. McMaster University, Box 2000, Stn. A, Hamilton, Ont., Canada L8N 3Z5.

Six healthy subjects performed maximal exercise for 30 s on an isokinetic ergometer at 60 and 140 rpm. Higher peak power was attained at 140 rpm (1473 ± 370 W) (mean ± SD) than at 60 rpm (1122 ± 139 W), but the decline in power was greater at 140 rpm (59.5 ± 4.5% vs 27.1 ± 7.5 %). Changes in the concentration of muscle metabolites were similar, creatine phosphate fell and glycolytic intermediates and lactate (La^-) increased at both velocities. Muscle [La^-] was 29.0 ± 3.98 (140 rpm) and 31.0 ± 4.31 (60 rpm) mmol/kg wet weight immediately post exercise. After 10 s exercise (n = 2), large similar changes were found in glycolytic intermediates and [La^-] (14.2 to 17.2 mmol/kg). After 30 s exercise, arterialized venous plasma [La^-] increased, initially unaccompanied by a fall in bicarbonate. Later in recovery, plasma [La^-] was higher following exercise at the higher frequency and muscle [La^-] was also higher, as were concentrations of glucose-6-phosphate and fructose-6-phosphate. We conclude that glycogenolysis is maximally activated at both pedal speeds; the greater fatigue at the higher speed is not accompanied by greater biochemical changes.

Supported by the Medical Research Council of Canada, the Ontario Ministry of Health and the Ontario Heart Foundation.

38.2

PLASMA VOLUME CHANGES WITH MAXIMAL LEG TRAINING IN EXPERIENCED WEIGHT LIFTERS. L.A. Kaminsky*, R.G. Knowlton*, J. Morrison* and R.K. Hetzler* (Spon: M.M. Sawka). Southern Illinois University, Carbondale, IL 62901

Ten male weight lifters who had trained no less than 2 years were studied while participating in a maximal squat training exercise. The mean maximal 1-RM leg strength was found to be 173± 29.2 kg. For this study the subjects completed 8 repetitions, 8 sets at 60% of 1-RM which totalled a mean of 6110± 992 kg lifted within 24 minutes. Subsequent to a period of sitting, plasma volume shifts (Hb, Hct) and serum protein concentration were determined after 20 minutes of standing and after sets 2, 4, 6, 8. At termination mean plasma volume had decreased by 17.9% from sitting values and plasma protein had increased by a mean of 2.8%. After the eighth set the rate pressure product had increased to 22.9 x 10^3 or 353% and terminal lactate was X = 70.4 mg%. A significant correlation, r = -0.72 was found between the total weight lifted and the final percent plasma volume change (Y = 8.776 - 0.004371 total weight lifted kg). Significant quadratic trends across time were found for plasma volume loss and the rate pressure product increase which indicated that the major physiological adjustment occurred early in the exercise. It was concluded that maximal leg exercise as typically engaged in by weight lifters offers a substantial perturbation to the cardiovascular system which implies a need for cardiovascular fitness as a prerequisite to such training.

38.3

CARDIOVASCULAR AND METABOLIC RESPONSES TO ISOMETRIC LEG EXERCISE PERFORMED VOLUNTARILY AND VIA ELECTRICAL STIMULATION. W.S. Sheldon* and R.M. Glaser, Wright State University School of Medicine, Dayton, OH 45435 and Rehab. Inst. of Ohio, Miami Valley Hospital, Dayton, OH 45409

To determine differences in cardiovascular and metabolic responses to graded isometric exercise of the quadriceps muscles performed voluntarily and via electrical stimulation, three able-bodied males volunteered to participate as subjects. Isometric exercise bouts were 4-min in duration and consisted of ten 2.5-sec contractions per min for each leg in an alternating pattern. Contraction force was monitored by a strain gauge transducer in conjunction with a computer. Leg extension force was progressive for each exercise bout (10,20,30 lb). Electrical stimulation of the muscles was accomplished by a closed-loop computer controlled stimulator using surface electrodes over motor points. This system automatically regulated contraction force and time. In comparing changes from rest for electrically induced vs voluntary exercise, respectively, we found higher $\dot{V}$ oxygen uptake (+59%, +44%) and arteriovenous O_2 difference (+49%, +24%), similar pulmonary ventilation (+58%, +63%) and heart rate (+9%, +7%), lower stroke volume (-2%, +8%) and cardiac output (+6%, +17%). These data suggest that increased aerobic metabolism during electrically induced leg exercise is supported predominantly by greater extraction of O_2 from the blood rather than a marked increase in the delivery of blood to the active muscles. (Supported in part by the VA)

38.4

AEROBIC AND ANAEROBIC ENERGY PRODUCTION DURING A PROGRESSIVE ISOTONIC EXERCISE. C.M. Ladd*, C.J. Gaebelein, and A.M. Moudy. St. Louis Univ. Med. Center, St. Louis, MO 63104

Alterations in blood flow, blood gases and pH in femoral venous blood from an exercising hindlimb were studied during a progressive isotonic exercise in rabbits anesthetized with urethane and chloralose. In one group, the cut sciatic nerve was stimulated at 1 Hz to induce plantar flexions at 2,5 and 8% of an afterload at which only isometric tension developed. Another group exercised at 30 and 50% of this value. The experimental session consisted of a series of 5-min non-exercise periods alternated with 6-min exercise periods, and a 10-min post-exercise period. Venous blood samples were obtained before the first exercise period, during the final minute of each exercise period, and 10-min after the final exercise period. Arterial blood samples were drawn periodically. No alterations in the variables studied were found in either arterial blood samples or venous blood samples from control animals. Exercise at all afterloads induced similar increases in blood flow and venous pCO_2, and decreases in venous pO_2. While pH was also decreased at all afterloads, a greater decrement was observed at the two heaviest afterloads. These results are consistent with previous data suggesting that the capacity of the gastrocnemius/plantaris muscle group to produce energy aerobically is limited even at relatively low exertion levels. This, in turn, may be due to the fiber type composition of this muscle group. (Supported by RR05388).

38.5

CHANGES IN MIXED VENOUS AND ARTERIAL BLOOD CONTENT DURING PROGRESSIVE ISOTONIC EXERCISE. A.M. Moudy, C.J. Gaebelein, C.M. Ladd* and J.M. Pivarnik. St. Louis Univ. Med. Center, St. Louis, MO 63104

Previously, increases in $[Na^+]$, $[K^+]$, and [lactate] were found in venous blood from an exercising hindlimb but not in blood from an inactive limb. To examine this discrepancy, alterations in these substances were studied in blood from either right ventricle (n=6) or descending aorta (n=8) in rabbits anesthetized with urethane and chloralose. Each experimental session consisted of 5-min non-exercise periods alternated with 6-min exercise periods, and a 10-min post-exercise period. During each exercise period, the cut sciatic nerve was stimulated to induce plantar flexion at 2,5,8,30 or 50% of an afterload at which only isometric tension could be developed. Venous blood samples were obtained during the final minute of pre-exercise as well as each exercise session, and 10-min after the final exercise period. Blood from descending aorta showed changes similar to those observed in that from inactive limb, while alterations in mixed venous blood were intermediate between those in active limb and those in descending aorta. Further, it appeared that the largest decrements in concentration occurred between active limb and right ventricle. Thus, the mixing of blood from active limb with that from inactive areas may play a greater role than either the pulmonary circulation or inactive muscle in preventing large ionic fluctuations in the general circulation during exercise. (Supported by RR05388 and HL26859).

38.6

THYMIC INVOLUTION AND ADRENAL RESPONSES IN THE SUSPENDED RAT MODEL FOR WEIGHTLESSNESS. J. M. Steffen and X. J. Musacchia. Department of Physiology & Biophysics, School of Medicine, University of Louisville, Louisville, Ky. 40292

Weightlessness produces changes in the immune system. Animal models of weightlessness also produce effects on the immune system, e.g., thymic involution and supression of interferon production. The purpose of this study was: to assess the extent of thymic involution in a whole body suspended rat; to determine the role of antiorthostatic (AO) positioning in thymic response; and, to evaluate the role of stress in thymic response by monitoring adrenal wt. and plasma corticosterone (PC). Male Sprague-Dawley rats (175-200g) were suspended in either an AO head-down tilt (15-20°) or orthostatic (O) position (Deavers et al, JAP 49:576-582, 1980). After decapitation, heparinized plasma was collected and stored at -20°C prior to RIA of PC. The Thymus and adrenals were excised and wet wt. and % water determined. Wet wt. of thymus was reduced by about 40% in AO and O rats when compared with age-matched metabolism cage (MC) controls. Changes in % water did not account for the altered tissue weights. Adrenal hypertrophy (+30% and +33% in AO and O rats, respectively, compared with MC) was evident in suspended animals. PC increased significantly on day 1 of suspension (37.3ug/100ml) compared with MC (14.1ug/100ml) but normalized (12.2ug/100ml) by day 7. The results document thymic involution in suspended rats and suggests that this may result from suppressive effects of glucocorticoids on the thymus. (Support: NASA Grant NSG-2325).

38.7

EARLY RIGHT ATRIAL PRESSURE CHANGES DURING SIMULATED WEIGHTLESSNESS IN RATS. Frank G. Shellock, Stanley A. Rubin, David Mickle,* Gabrielle Nevitt,* and H.J.C. Swan. Cedars-Sinai Medical Center, Los Angeles, Ca. 90048

The antiorthostatic, hypokinetic (ie. head-down suspension, H-DS) rat is used to simulate the circulatory effects of weightlessness. However, little is known about the early cardiovascular adaptive responses associated with this animal model and the effects of varying degrees of H-DS. Therefore, the purpose of this study was to characterize the acute right atrial pressure response to two different levels of H-DS. Unanesthetized, unrestrained, female Sprague-Dawley rats (wt 309±32 gms) with chronically implanted right atrial (RA) catheters were subjected to either a mild (Group A, N=6) or severe (Group B, N=5) level of H-DS utilizing the tail-traction technique.

	CTL	1hr	2hr	3hr	4hr	5hr	6hr	7hr	8hr	24hr
Group A	1±1	4±1*+	4±1*+	3±1*+	3±1*+	3±1*+	3±1*+	3±1*+	3±1*+	2±1+
Group B	2±1	7±1*	6±1*	6±1*	5±1*	4±1*	4±1*	4±1*	4±1*	5±1*

(RA pressure-mmHg, CTL-control, M±SD,* $p<0.05$-values compared to control, +$p<0.05$ Group A compared to Group B)

Group A rats had less of a central fluid shift and appeared to be adapting to H-DS earlier than Group B rats. We conclude that the level of H-DS significantly effects early RA pressure changes and the adaption to simulated weightlessness in rats.

LUNG FLUID BALANCE AND PULMONARY CIRCULATION I

39.1

PULMONARY CAPILLARY FILTRATION COEFFICIENT DURING PROSTAGLANDIN INFUSION. W.F. Hofman and I.C. Ehrhart. Department of Physiology, Medical Georgia, Augusta, GA 30912

We determined the effect of continuous prostanoid infusion upon the pulmonary capillary filtration coefficient (K_f) in the isolated dog lung. Lower left lobes (LLL) obtained from mongrel dogs were cannulated, ventilated and pump perfused at constant flow (6.1±0.2 ml/g LLL) with autogenous blood. Airway and vascular pressures were monitored along with LLL weight. One group of LLL's (n=6) was continously infused with $PGF_{2\alpha}$ (Tromethamine salt) in saline at a rate of 216±18 ng/min/kg body wt. and another group (n=5) received PGI_2 (Prostacyclin, sodium salt) in Trizma buffer at the rate of 363±25 ng/min/kg body wt. Control lobes (n=5) were continuously infused with saline or Trizma buffer at a rate of 0.21 ml/min. None of the infusions significantly altered pulmonary vascular resistance. Approximately 1 hr from the start of the infusion, a K_f was determined as the slope of the relationship between rate of LLL weight gain and capillary pressure elevated in a stepwise fashion (J. Appl. Physiol. 56: 862, 1984). The K_f's ($ml \cdot min^{-1} \cdot mmHg^{-1} \cdot 100g$ LLL^{-1}) for each group are tabulated below (mean±SEM).

	Control	$PGF_{2\alpha}$	PGI_2	p
K_f	0.09±0.01	0.08±0.01	0.09±0.03	>0.05

At the dosages infused, neither $PGF_{2\alpha}$ nor PGI_2 altered pulmonary vascular permeability or resistance in the LLL. (Supported by BRSG #S-07RR5365-23)

39.2

MICROVASCULAR PRESSURE (Pc) UNCHANGED BY ELEVATED PULMONARY ARTERIAL PRESSURE (P) AFTER LUNG EMBOLISM (E). Ehrhart, I.C., J.E. Hall* and W.F. Hofman. Medical College of Georgia, Augusta, GA 30912.

We reported that P did not increase rate of weight gain after E of the isolated dog lung lobe (LLL) perfused with anticoagulated blood (Fed. Proc. 42:1275, 1983). P was poorly transmitted to microvessels due to the E associated increase in upstream vascular resistance (Rup). Since E is usually accompanied by blood coagulation, we examined the effect of P on Pc and permeability after embolizing the lung lobe with 100-μm glass beads prior to lobectomy. After E, lobe blood was positive for fibrinogen degradation products. The LLL was ventilated and perfused at either high P (HP,n=6), or low P (LP,n=6). A capillary filtration coefficient (Kf) was obtained by stepwise pressure elevation. Ratio of Rup to total vascular resistance (PVR) and Pc were obtained by venous occlusion. Data 2 h after E are given (*, $p< 0.05$).

		LP	HP
Pa	Torr	26.0 ± 0.7	51.8 ± 4.0*
PVR	$Torr \cdot min \cdot ml^{-1}$	0.244 ± 0.082	0.197 ± 0.050
Rup/PVR		0.85 ± 0.05	0.86 ± 0.03
Pc	Torr	7.6 ± 1.5	9.4 ± 1.3
Kf	$ml \cdot min^{-1} \cdot 100g^{-1} \cdot Torr^{-1}$	0.18 ± 0.03	0.27 ± 0.08

Even in the presence of blood clotting, high P did not elevate Pc or further increase lung permeability (Kf) following E. (Supported by BRSG #S-07RR05365-23)

39.3

CARDIOPULMONARY RESPONSES TO ENDOTOXIN IN PONIES. N.C. Olson*, R.E. Meyer*, D.L. Anderson*(SPON: C.E. Stevens). School of Veterinary Medicine, North Carolina State University, Raleigh, North Carolina 27606.

Endotoxemia in the horse is believed to be a frequent complication of gastrointestinal disorders and may lead to cardiopulmonary dysfunction. We evaluated the effects of endotoxemia on cardiopulmonary parameters in halothane-anesthetized ponies maintained in sternal recumbency and spontaneously breathing 100% O_2. E.coli endotoxin (E) was infused intravenously at 20 µg/kg for 1 hr followed by 10 µg/kg the subsequent 4 hrs. Cardiac index (CI), lung extravascular thermal volume (ETV_L) and central plasma volume (CPV) were determined by the thermal-dye technique. By 15 min after onset of E, stroke volume (SV) and CI decreased while mean pulmonary artery pressure ($P_{\overline{PA}}$), pulmonary vascular resistance (PVR), physiological deadspace (V_D/V_T) and $\dot{V}_E$ markedly increased. Pretreatment with flunixin meglumine (1.1 mg/kg bolus plus .55 mg/kg/hr) abolished these early effects. By 30-60 min SV, CI, $P_{\overline{PA}}$, PVR, $\dot{V}_E$, and V_D/V_T returned to baseline values in endotoxemic ponies. However, by 60-120 min E caused a sustained decrease in SV, CI and CPV while PVR increased. ETV_L at 5 hrs, postmortem gravimetric lung water and bronchoalveolar lavage albumin were unchanged in all ponies. We conclude that endotoxemia in the equine causes pulmonary dysfunction that is mediated in part by cyclooxygenase metabolites but that pulmonary edema does not occur.

39.4

COLLOID OSMOTIC PRESSURE (COP) PRODUCTION BY BOVINE SERUM PROTEINS IN NORMAL AND HYPOPROTEINEMIC STATES: IN VITRO MODELS AND IN VIVO RESPONSES. Rebecca L. Nichelson* and James F. Amend. University of Nebraska-Lincoln, Lincoln, NE 68583-0905

A relationship may exist between presence of excess extravascular fluid in the lung, and relative susceptibility to respiratory disease in calves. Alterations in total protein and albumin-globulin ratio (A/G) occur in stressed cattle of all ages. These events potentially may depress COP, and concurrently the removal of extravascular fluids from lung tissue. We studied COP production in vitro by preparing simulated bovine serum from isotonic Ringer's solution and bovine serum protein fractions which were weighed and combined in appropriate proportions. We examined COP production in vivo by collecting serum samples from a large population of dairy and beef calves. COP was measured with a Wescor colloid osmometer. Total protein and albumin were measured by biuret and bromcresol green methods, respectively. Sample pH was determined with an IL 713 blood gas analyser. It was possible, using total protein, % albumin, and pH as variables, to define models which predicted in vitro COP in normal and hypoproteinemic states. These variables were then obtained from calf samples, and used to predict COP for calf sera by using the models. Actual measured COP from the calf sera was then compared to model prediction. The models proved useful in predicting in vivo COP, provided pH was maintained by careful sample handling. (This study was supported in part by USDA #59-2111-0-061-01, and by resources of the Agricultural Research Division, IANR, U. Nebr.-Lincoln.)

39.5

EFFECT OF HISTAMINE ON CAUDAL MEDIASTINAL NODE (CMN) EFFERENT LYMPH FLOW IN SHEEP. K.Koike*, S. Yamada* and N.C. Staub. Cardiovasc Res Inst and Dept Physiol, Univ California, San Francisco, CA 94143

Is the increase in lung lymph flow during 4h intravenous histamine infusion (ARRD 120:875, 1979) due to increased permeability of the CMN (AJP 245:H553, 1983)? We tested this possibility by removing all lung afferent lymph to the node (PHYSIOLOGIST 24:A55, 1983). In 8 anesthetized, ventilated, prone sheep, after a 2h baseline, we cut both pulmonary ligaments and cauterized the lung hilar lymphatics. After 2h more, we raised left atrial pressure (Pla) or infused histamine [3 µg base/(kg x min)] for 2h. We measured CMN efferent lymph flow by weight (g/15 min). The data are summarized in the table (mean ± S.D.).

Condition	†Pla	Histamine
Baseline	1.07 ± .02	1.17 ± .67
Cut Lymphatics (2h)	.21 ± .15	.41 ± .26
Experiment (2h)	.19 ± .10	.36 ± .26

On average, cutting the pulmonary lymph afferents reduced CMN flow by 72%. Increased left atrial pressure did not affect lymph flow; proving complete lung deafferentation of CMN. Histamine also had no effect. The increase in CMN efferent lymph flow seen with continuous histamine infusions comes from the lungs. Supported by HL25816 (Program Project).

39.6

EFFECT OF CONTINUOUS-FLOW PLASMAPHERESIS ON LUNG LIQUID CONDUCTANCE IN AWAKE SHEEP. P.M. Dodek, T.W. Rice*, M.R. Bonsignore*, and N.C. Staub. Cardiovasc Res Inst & Dept Physiol, Univ of Calif, San Francisco, CA 94143.

The process of plasmapheresis and not hypoproteinemia causes the observed increase in lung liquid conductance after batch plasmapheresis (FED PROC 43:1032, 1984). To determine whether a different method of plasmapheresis affects lung liquid conductance, we did control (SHAM plasmapheresis) and protein removal (REAL plasmapheresis) experiments using a continuous-flow membrane filter (Amicon Corp) in six awake sheep. Lung lymph flow (L), plasma protein concentration (P), and lung liquid conductance divided by the baseline value (K/Kb) for baseline and four periods after plasmapheresis are shown in the table (mean±SD).

	L(ml/15min)		P(g/dl)		K/Kb	
Condition	SHAM	REAL	SHAM	REAL	SHAM	REAL
Baseline	1.9±1.1	1.8±0.9	5.6±.4	5.7±.7	1	1
0-4h	2.7±1.4	4.8±1.9	5.2±.5	3.3±.5	1.2±.3	2.1±1.2
13-17h	1.9±1.0	2.7±0.9	5.6±.6	4.1±.5	1.0±.3	1.1±0.4
23-27h	1.8±1.0	2.4±1.1	5.7±.5	4.5±.4	1.0±.3	1.1±0.5
38-42h	1.7±1.0	1.9±0.7	5.8±.7	4.8±.5	0.9±.3	1.0±0.5

Lymph flow increased more after protein removal but conductance was not different between groups. Like batch plasmapheresis, continuous-flow plasmapheresis causes a transient increase in lung liquid conductance, independent of hypoproteinemia. [Supported by HL25816 (Prog Proj); ALA, MRC, and Parker B. Francis Fellowships]

39.7

COMBINED EFFECTS OF EPINEPHRINE, OXYGEN, AND OXYGEN DEPRIVATION ON PULMONARY HEMODYNAMICS. Ronald C. Elkins, Mary M. Lane* Rene B. Willis*, Cynthia K. Murray*, David M. Keyes * University of Oklahoma, Oklahoma City, OK 73104

The effects of epinephrine on hemodynamics in the presence of altered levels of oxygenation were studied in 12 dogs. In dogs ventilated with room air and infused continuously with epinephrine for 15 minutes at 4 ug/kg/min, increases were observed for femoral artery pressure(FAP)(146.4±5.7 to 195.5±13.0 mmHg, $p<.03$), cardiac output (CO)(2033+358 to 3289+994 l/min, N.S.), heart rate (HR) 147±6 to 154±8 bpm, $p<.05$), and mean pulmonary artery pressure (PAP)(16.1±1.8 to 22.2±2.9 mmHg, $p<.05$). The same effects were noted for hyperoxia (P02±160 torr). A significant enhancement ($p<.01$) of the epinephrine-induced rise in PAP was seen under hypoxic conditions, PAP rising from 24.8±2.1 to 35.2±4.8 mmHg, $p<.02$. Hypoxia (P02±55 torr) also seemed to induce a drop in the mean left atrial pressure (LAP) with epinephrine, from 8.0±1.8 to 5.8±2.1 mmHg ($p<07$), not seen in ventilation with room air, and prevented the increase in heart rate seen in normoxia. Related to these effects, pulmonary vascular resistance (PVR) was observed to rise slightly with epinephrine in the hypoxic state but not in normoxic or hyperoxic states. In hypoxia with epinephrine PVR rose from 11.8±3.4 to 15.4±4.8 torr/l/min. These data suggest that epinephrine should not be used in the hypoxic patient or in patients with significant right ventricular compromise.

39.8

PLATELET ACTIVATING FACTOR (PAF) DEPRESSES PULMONARY VASCULAR REACTIVITY IN ISOLATED, BUFFER PERFUSED RAT LUNGS. Bruce D. Bowdy*, Carol N. Reinsel*, and Mark N. Gillespie*. (SPON: L. Diamond). University of Kentucky, College of Pharmacy, Division of Pharmacology and Toxicology, Lexington, KY 40536.

Lung injury induced by monocrotaline or α-naphthylthiourea is associated with enhanced pulmonary vascular responsiveness to spasmogens. Since PAF also provokes lung injury and because this agent has been reported to augment reactivity in isolated peripheral blood vessels, we tested the hypothesis that PAF enhances pulmonary responsiveness to vasoconstrictor stimuli. Lungs were isolated from male rats and perfused at constant flow in a recirculating manner with physiologic salt solution containing 3% albumin. Pressor responses evoked by angiotensin-II (Ang-II; 0.1, 0.5 or 1.0 µg i.a. bolus injections), hypoxia (3%O_2), and KCl (15 or 30 mg i.a. bolus injections) were compared between preparations in which either PAF (0.1 to 1 µg/ml) or its vehicle had been added to the perfusate reservoir. None of the concentrations of PAF enhanced responses to any of the constrictor stimuli. At the 1.0 µg/ml PAF concentration, responses evoked by both Ang-II and hypoxia were attenuated relative to control whereas KCl-induced vasoconstriction was unaffected. Wet weight-to-dry weight ratios were larger than control in PAF-treated lungs exhibiting depressed responsiveness. We conclude that PAF does not enhance pulmonary vascular reactivity in isolated rat lungs and, in concentrations that provoke edema, may in fact attenuate vascular responsiveness to some spasmogens.

39.9

THE EFFECTS OF AGING ON HYPOXIC PULMONARY VASOCONSTRICTION. T.J. Gregory*, M.W. Chapleau, W.R. Summer* and M.G. Levitzky. LSU Medical Center , New Orleans, La. 70112.

We sought to investigate the effects of aging on hypoxic pulmonary vasoconstriction in young adult and adult animals. Lungs from 4 month and 7 month old ferrets were isolated and perfused at 40 ml/min. The lungs were sequentially ventilated with 21%, 19%, 12%, 10%, 8%, 6%, 4%, 8% and 21% O_2 with 5% CO_2 to obtain hypoxic pulmonary vasoconstriction dose response curves. At 21% O_2, mean pulmonary arterial pressure was 12.8 ± 0.7 Torr in both age groups. The 4 month old lungs exhibited a prompt and vigorous hypoxic pulmonary pressor response. This response was first observed at 10% O_2 as a 4.1 + 1.4 Torr increase in mean pulmonary arterial pressure. At 4% O_2, mean pulmonary arterial pressure increased to 62.0 ± 2.8 Torr. In the 7 month old lungs, hypoxic pulmonary vasoconstriction was not observed until the inspired O_2 was decreased to 6% where mean pulmonary arterial pressure increased 7.3 ± 2.5 Torr. At 4% O_2, mean pulmonary arterial pressure increased to only 43.8 ± 2.0 Torr. These data suggest that the strength of hypoxic pulmonary vasoconstriction decreases with age. This finding may help to explain the ventilation-perfusion imbalances and decreased arterial oxygen tension observed in elderly people.
(supported by Grant HL 29042)

39.10

HEMODYNAMIC RESPONSE TO TEMPORARY UNILATERAL PULMONARY ARTERY OCCLUSION (TUPAO) IN DUCKS. Frank L. Powell, Randolph H. Hastings and Robert W. Mazzone. Department of Medicine, University of California, San Diego, La Jolla, CA 92093.

We investigated TUPAO in 5 anesthetized artificially ventilated Pekin ducks (2.65 to 3.53 kg) by inflating a Swan-Ganz balloon or tightening a snare. Upon TUPAO, mean pulmonary artery pressure increased from 12.8±1.0 to 23.9±1.8 mmHg and upon release returned to 13.0±0.9 mmHg (±sem). In one duck, we also measured mean left atrial pressure (LA) from a cannula inserted through the atrial wall. Upon TUPAO, LA increased from 4.3±1.0 to 8.3±1.5 mmHg, and upon release returned to 3.8±0.8 mmHg (3 trials). Cardiac output measured in this bird by the Fick method averaged 0.96 L/min in control conditions, and 0.92 L/min with TUPAO. Thus, TUPAO increased PVR by 50%. We investigated the effect of TUPAO on the structure of the air-blood capillaries in the lung by a stereologic analysis of transmission electron micrographs of rapidly frozen lungs from a domestic goose (4.6 kg). The percentage of exchange tissue occupied by air and blood capillaries were 60 and 27% respectively in the occluded lung and 36 and 48% in the lung with twice normal perfusion. Thus, there is a finite compliance in the avian pulmonary circulation but it is less than in mammals. This may be important if DLO_2 does not increase and blood capillary transit time decreases with increased blood flow because distension/recruitment of blood capillaries are limited. Supported by NIH RO1 HL26050.

39.11

EFFECTS OF DOBUTAMINE ON PULMONARY HEMODYNAMICS. M.M. Lane*, R.B. Willis*, D.M. Keyes*, C.K. Murray*, Ronald C.Elkins. University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma 73104

The role of inotropic agents in supporting the systemic circulation is well documented, but the effects of such drugs on the pulmonary vascular bed are less studied. The effects of dobutamine (DOB) on the systemic and pulmonary circulation of 12 dogs were studied in the presence of normal arterial oxygen tension (NRM), hypoxia (HPX) and hyperoxia (HPR). Although systemic vascular resistance (SVR) was significantly reduced by 15 minutes of DOB infusion at 10 ug/kg/min in all three states (NRM, HPX, HPR), e.g. from 82.9±16.5 to 57.6±13.4 torr/l/min for NRM ($p<.01$), HPX alone elevated SVR (101.7±22.7) so that the reduction in SVR by DOB was greater for HPX dogs (to 67.3±12.5, $p<.005$). No change in pulmonary vascular resistance was noted during DOB infusion. Systolic PAP significantly increased with DOB during NRM and HPX (from 29.3±3.8 to 40.0±6.8 mmHg, $p<.02$ and 27.2±3.4 to 41.5±10.3 mmHg, $p<.05$) but this increase appeared to be significantly inhibited ($p<.05$) by HPR (28.4±5.2 to only 34.4±8.6 mmHg). Cardiac output increased with DOB in NRM (1.7±0.2 to 2.3±0.4 l/min. $p.<05$) and HPX (1.5±0.4 to 2.1±0.5 l/min) but did not change under HPR. These results indicate that level of oxygenation does affect the action of DOB on hemodynamics. Such interactions should be considered in the selection of an inotropic agent in the clinical setting, as the desired beneficial effect may be inhibited or an undesired effect produced.

39.12

CANINE HEARTWORMS (DIROFILARIA IMMITIS) ATTENUATE HYPOXIC PULMONARY VASOCONSTRICTION. M.W. Chapleau and M.G. Levitzky. Dept. of Physiology, LSU Medical Center, New Orleans, LA 70112

Dogs, shown to be free of microfilaria (peripheral blood smear), were anesthetized, vagotomized, mechanically ventilated and paralyzed. Separate ventilation to each lung was attained via a dual-lumen endotracheal tube inserted through a tracheostomy. Electromagnetic flow probes were placed on the left ($\dot{Q}_L$) and main ($\dot{Q}_T$) pulmonary arteries, and catheters placed in the pulmonary artery, left atrium and aorta. Unilateral alveolar hypoxia was achieved by ventilating the left lung with 100% nitrogen while maintaining 100% oxygen ventilation to the right lung. At autopsy, the right ventricle and pulmonary arteries were opened and checked for the presence of adult heartworms. In the heartworm free dogs (HWF, n=5), the fraction of the cardiac output perfusing the left lung ($\dot{Q}_L/\dot{Q}_T$) decreased by 31±5 % during left lung hypoxia. Dogs with heartworms (HW, n=5) demonstrated an 11±6 % decrease in $\dot{Q}_L/\dot{Q}_T$, which is significantly less than the decrease seen in HWF dogs. There was no significant difference in pulmonary artery pressure or cardiac output between HW and HWF dogs. These results indicate that Dirofilaria immitis infestation attenuates the ability of hypoxic pulmonary vasoconstriction (HPV) to redistribute pulmonary blood flow. This attenuation of HPV is not related to changes in pulmonary artery pressure or cardiac output. (Supported by NIH HL 29042 and Sigma Xi).

39.13

PULMONARY VASCULAR REACTIVITY OF THE NEWBORN PONY FOAL. W.H. Drummond, I. Sanchez*, P.C. Kosch*, A.I. Webb*, H.H. Shrager*. University of Florida Colleges of Medicine and Veterinary Medicine, Gainesville, FL 32610

Adult ponies develop pulmonary hypertension at altitude (Will, 1975), but the neonatal response to hypoxia is unknown. Four pony foals age 5 days were instrumented with a systemic (SA) and a Swan-Ganz pulmonary artery (PA) catheter, during anesthesia and tracheal intubation. Cardiac output (CO), PA and SA pressure (PAP, SAP) were measured as the foals breathed gas mixtures with F_iO_2 .08 to .94. Mean SAP was 97±17.6 mmHg(SD), and mean diastolic pressure 59±13 mmHg. SAP did not vary with ΔPaO_2. Mean PAP was 27±14 mmHg at PaO_2 of 70-140 Torr, and rose to 44±20 mmHg ($p<.01$) as PaO_2 fell. CO was 131±26 ml/kg/min at PaO_2 of 70-140 Torr. When PaO_2 was <45 Torr mean CO was 176±42 ml/kg/min ($p<.02$). Since foramen ovale or ductus arteriosus shunt might have altered thermodilution CO measurements, and since we had no left atrial pressure measure, we compared PAP to SAP to define relative reactivity of the two circulations. Two foals (#2 & #27; full sibs) had very marked elevation of PAP/SAP to 0.6-1.0 at low inspired oxygen tensions. Two different foals (half sibs of #2 & #27) attained maximal PAP/SAP of only 0.2-0.4 at similarly low oxygen tensions ($p<.05$ by analysis of covariance). The PAP/SAP data for foals #2 and 27 were outside the normal range for lamb neonates of 2-6 days old. Thus, pulmonary vascular reactivity to ventilatory hypoxemia varied greatly in pony foals. It may be that the sibship of mare #39 had exaggerated reactivity to hypoxemia, suggesting that, as in cattle, a genetic predisposition for reactive pulmonary hypertension exists within some pony genomes.
Sponsored by: Florida Thoroughbred Breeders Association.

40.1

ERYTHROCYTE DEFORMABILITY IN RATS DURING RECOVERY FROM HEMOLYTIC ANEMIA. James M. Norton. Univ. New England, Biddeford, ME 04005.

Deformability is an important determinant of RBC lifespan in normal and pathologic states. The deformability of rat erythrocytes during and following hemolytic anemia produced by phenylhydrazine (PHZ) was studied by measuring flow rates of suspensions of washed RBCs (80 million cells/ml) drawn through three and five-micron filters by a -20 cm H2O pressure gradient. Electronic cell sizing provided volume distribution data for these suspensions and for subpopulations of RBCs separated according to density by centrifugation. The acute anemia produced by PHZ was characterized by a 39% reduction in hct and an extensive (86.7%) and homogeneous reticulocytosis with an MCV of 101 cubic microns (twice normal rat MCV) associated with a significant reduction in deformability measured by filtration. These macrocytes demonstrated a mean lifetime of 26.6 days with little evidence of intravascular remodeling. MCV was reduced toward normal by selective removal of the macrocytes and a restoration of reticulocyte volume to normal (58 cubic microns) over a four week period. Increases in deformability during recovery were significantly correlated with reductions in both reticulocyte count and sample MCV. Restoration of normal erythrocyte deformability was felt to be specifically related to the disappearance of the stress macrocytes from the circulating RBC population. (supported by the Kroc Foundation and AHA/Maine Affiliate, Inc)

40.2

THE CYTOSKELETAL ELEMENTS IN CELL-TO-CELL RECOGNITION AND INTERACTIONS. Anwar A.Hakim, Charles M. Sirakis, and Charles E. Josph*. Loyola Univ. Med.Center, Maywood, Illinois 60153, and the Univ. Southern Calif. School of Dentistry, Los Angeles, California 90007.

Earlier studies by Hakim and Joseph reported the protective action of fibronectin (Fn) against the effects of adenosine-5-triphosphate (ATP) on human skin and gingival fibroblasts(Expt. Cell Biol. 51:96 108, 1983). The sequence of events associated with the interaction of cytotoxic-T-lymphocyte(CTL) and its target cells (TC) include recognition of TC by CTL; CTL-TC binding; programming of the TC for lysis; target dissolution and recycling of the CTL. The present studies report on the oxidative activation of Galactose terminals(GT) at the TC surface signals its recognition by the CTL.Human Peripheral Blood Lymphocytes (HPBL) were used as the effector cell and various human neoplastic cells as the TC-cells.Neuraminidase(VCN) and PHA activate the GT at the TC and CTL surfaces, are the recognition signals. ATP alters cellular microtubule-tubulin equilibrium, induce aberration in the CTL cell morphology, thus inhibits CTL-TC-binding. On the other hand, (Fn)stabilizes the cytoskeletal elements equilibrium and protects from ATP inactivation. Therefore, the cytoskeletal elements and the cell surface glycoproteins modulate CTL function.

40.3

CHEMICAL SHIFT OF WATER IN PELLETS OF TUMOR CELL CLONES OF DEFINED METASTATIC POTENTIAL. Steven D. Bines*, Stephen P. Tomasovic*, James Frazer*, Arthur W. Boddie, Jr.* (SPON: Robert Vick). UTSCC-M. D. Anderson Hospital and Tumor Institute, Houston, Texas 77030.

Three rat 1376NF mammary adenocarcinoma clones of either high (MTLn3), intermediate (MTC) or low (MTPa) in vivo metastatic potential were grown in Roller tissue culture. Approximately $1.5x10^8$ cells were then centrifuged to form a $0.5cm^3$ pellet in the tip of a spectrometer tube for analysis in a Varian EM360L NMR spectrometer operating at 60.0 MHz: seven replicates of MTLn3, five replicates of MTC, and five replicates of MTPa were examined. The mean value for the water peak was 5.14+.0301ppm for the highly metastatic replicates, 5.07+.0207 for the replicates of intermediate metastatic potential and 5.05+.0095 for the replicates possessing low metastatic potential. The difference in shift between MTLn3 and MTC or MTPa was significant ($p<.001$). The difference between MTC and MTPa was not statistically significant. The relationship between spectral differences and any biological properties of the clones are unknown. However, qualitative and quantitative differences in cell surface glycoproteins exist between these clones and this preliminary study suggests that NMR spectroscopy may detect differences in tumor cell clones which may be relevant to their phenotypic properties.

40.4

ACTIVATION AND INHIBITION OF THE Na/K/Cl COTRANSPORTER IN FERRET ERYTHROCYTES. H.C. Palfrey* (SPON: M. Field). Dept. of Pharm. & Phys. Sci., Univ. of Chicago, Chicago, IL 60637, USA

Ferret red cells possess a bumetanide-sensitive Na-K cotransport system (Flatman: J. Physiol. 341, 545, 1983). Here the dependence of the system on anions and its responses to cAMP have been examined. Erythrocytes from female ferrets had a cotransport (bumetanide-inhibitable)-mediated influx of K (^{86}Rb tracer) of 5-8 mmol/l/hr. This flux was absent when Cl was replaced with gluconate, methylsulfate, NO_3, SO_4 or SCN, but was present with Br. The titration curves for cotransport rate vs. extracellular Cl were different depending on the substituting anion used: NO_3, SO_4 and $MeSO_4$ yielded almost linear relationships in the range of 0-150 mM Cl, but the curves with gluconate and SCN were markedly sigmoid. The latter effect may be due to inhibition of cotransport by these anions and suggests caution in the interpretation of anion substitution data. Two anions were anomalous in that they appeared to stimulate cotransport in the presence of Cl: addition of HCO_3 or F led to a concentration-dependent increase in diuretic-sensitive K influx (2-3 fold at concentrations of 20 mM). However, the HCO_3 effect did not occur in SITS-treated cells, whereas the F effect remained intact. This suggests that HCO_3 enters the cell via the anion exchanger to exert its stimulatory effect. Preincubation of cells with 8BrcAMP (1 mM) inhibited cotransport by 40%. These results suggest that ferret red cells possess an Na/K/Cl cotransporter analogous to that found in avian erythrocytes, but that the effects of cAMP on the two systems are opposite.

40.5

KINETICS OF CL-DEPENDENT K INFLUX OF THE HUMAN ERYTHROCYTE IN THE PRESENCE AND ABSENCE OF EXTERNAL SODIUM. D.M. Kaji* and T. Kahn. Dept. of Med., Vet.Adm. Med.Ctr., Bronx, N.Y. 10468 and Mount Sinai School of Medicine, New York, N.Y. 10029.

A portion of the ouabain insensitive Cl-dependent K influx has been shown to occur in the absence of external Na (Na_o) and may represent KCl cotransport. We investigated the kinetics of this transport system with respect to external K (K_o) and stimulation by N-ethyl maleimide (NEM). The chloride dependent influx was measured in anion equilibrated fresh cells using 86Rb in the presence of ouabain and calculated as the difference in the presence of Cl and NO_3. Results: 1)The affinity for external K is significantly diminished in the absence of Na_o, as compared to Na media ($K^1/_2$=24±3mM v/s 8±2mM). 2)Na-augmented portion of K influx (K influx in Na media-K influx in zero Na_o) contributes 50% of the total K influx at Ko < 5mM but its contribution drops to 20% or less at Ko=30mM in many individuals. 3)NEM 0.5mM, in the absence of Na_o stimulates Vmax sixfold but the $K^1/_2$ for Ko is unchanged (27±5mM). Conclusions: 1)The putative KCl transport pathway in human red cells has a low affinity for external K in the absence of Na_o. 2)NEM stimulates this pathway several fold, but the affinity for Ko is unchanged. These findings are similar to those seen in LK sheep red cells. 3)External Na may have a complex interaction with the KCl cotransport pathway. (Supported by General Medical Research, Veterans Administration.)

40.6

REGULATION OF GASTRIC ACID SECRETION BY MODULATION OF A CHLORIDE CONDUCTANCE.

John Cuppoletti* and George Sachs UCLA Dept. Med. and CURE, VA Wadsworth, Los Angeles, CA 90073.

Gastric microsomal vesicles were obtained from resting and stimulated rabbit stomachs. Ionophore independent proton transport and rapid net uptake of K+ and Cl- were only observed in stimulated vesicles. Using isotope exchange and the fluorescent potential sensitive dye, 3,3 dipropylthiacarbocyanine, K+ and Cl- conductances were observed. Ionophore independent H+ transport appeared to be due to elevated Cl- permeability. Changes in K+ permeability could not be ruled out. H+ transport and K+ stimulated ATPase were both inhibited by furosemide (K 0.5=0.5 mM), and other anion site inhibitors. This inhibition was overcome by valinomycin plus high Cl-, and nigericin, respectively. Cl-, but not K+, conductance and self exchange activities were furosemide sensitive. Only the K+ conductance was sensitive to Mg-vanadate, suggesting close association of the K+ conductance with the (H + K)ATPase. These results suggest that H+ secretion is largely regulated via modulation or associaton of a furosemide sensitive Cl- conductance with the parietal cell apical membrane. **Supported by NIH AM 17328-11 & VA SMI award.**

40.7

THE (H,K)-ATPase: RECONSTITUTION OF THE H^+ PUMP. R.D. Gunther*, S. Bassilian* and E.C. Rabon* (SPON: G. Sachs). CURE/UCLA and VA Wadsworth, LA, CA 90073

H+ transport in native hog gastric microsomes occurs via a functional H+/K+ exchange. We have initiated tests of the hypothesis that the enzyme protomer functions as both H+ and K+ pump. The (H,K)-ATPase was solubilized in 0.9 to 1.5% cholate and collected as the 100,000 x g supernatant fraction following centrifugation in K+ buffer. This solubilized enzyme was reconstituted into both phosphatidylcholine:cholesterol (55/45) and phosphatidylcholine:cholesterol:phosphatidylethanolamine (44/36/20) liposomes by a sonication/cholate-dilution technique. MgATP dependent reconstituted H+ transport was demonstrated in Cl^- free K+ media. Optical probes of ΔpH and $\Delta\psi$ suggest a luminal K+ requirement and H+ transport via a neutral H+/K+ exchange. Sucrose gradient resolution of the reconstituted H+ transporter indicate a small fraction of the total phospholipids and solubilized enzyme population is reconstituted. ATPase activity of the soluble enzyme was stimulated by added phospholipids. The ATPase activity correlated with the H+ transporter exhibited both K+ and (K+ plus nigericin) stimulation. As in the native enzyme, the H+ transport reaction was relatively vanadate sensitive and oligomycin insensitive. This work was supported by NIH grant AM 17328-11, Veterans Administration and an SKB Fellowship.

CEREBRAL CIRCULATION

41.1

SUPERIOR CERVICAL SYMPATHETIC NERVE ACTIVITY IN STROKE PRONE SHR: A LINK TO STROKE? Shirley M. Mueller and William L. Black, Jr.* Indiana University School of Medicine, Indianapolis, IN 46202.

To determine the relationship between superior cervical sympathetic nerve activity and susceptibility to stroke, we measured superior cervical sympathetic nerve activity in the stroke prone substrain of the spontaneously hypertensive rat (SP-SHR), the spontaneous hypertensive rat, not stroke prone (SHR) and their normotensive control, Wistar Kyoto (WKY). The mean arterial pressure of the SP-SHR (181±6mmHg, mean±SE) and SHR (191±11)did not differ but both were significantly elevated over WKY (107±6, $p<0.001$). Cerebral ischemia was used to ilicit maximal sympathetic nerve activity. The increase in nerve activity from the resting state was significantly less in SP-SHR (101±11 uvolts, $p<0.001$) compared to SHR (229±10). WKY (105±18) reacted like SP-SHR. This diminished sympathetic capacity in stroke prone SHR compared to SHR, not stroke prone may contribute to their predisposition to stroke because of the failure of superior cervical sympathetic nerves to protect cerebral vessels during acute hypertension.

41.2

CAPILLARY MEAN TRANSIT TIME, REGIONAL CEREBRAL BLOOD FLOW, AND REGIONAL CEREBRAL BLOOD VOLUME AFTER RECOVERY FROM TOTAL CEREBRAL ISCHEMIA IN DOGS, S. A. Romeo*, K. A. McCracken*, R. C. Crumrine*, D. L. Jackson* and J. C. LaManna. Univ. Hospitals of Cleveland and Case Western Reserve Univ. Med. Sch., Cleveland, OH 44106

During recovery from total cerebral ischemia (TCI) there is a brief hyperemia, followed by diminishing cerebral perfusion. To study the degree of impaired reperfusion, 8 min of TCI was induced by inflation of intravascular occlusion balloons in the inferior vena cava and the aortic arch of thiopental anesthetized dogs. Capillary mean transit time (MTT) of a 1 ml bolus of 6% Hetastarch in normal saline was determined by optical monitoring, at 590nm by reflectance photometry, through a cranial window. RCBF was determined by radiolabeled microspheres in the cortex within the window. From these two parameters, regional cerebral blood volume (RCBV) was calculated by the Stewart-Hamilton equation, RCBV=RCBF*MTT. Pre-TCI RCBF was 41 ml/100g/min, MTT was 4 sec., and RCBV was 2.7 ml/100g. RCBF 1 hr after resuscitation from 8 min TCI was decreased by half and MTT was increased by 40%. RCBV was decreased by 30%. These results indicate long term impairment of cerebral perfusion even after a short period of TCI. Supported by NIH grant, RO1-HL23582.

41.3

THE EFFECT OF ANESTHESIA AND BLOOD FLOW ON REGIONAL BLOOD-BRAIN GLUCOSE TRANSPORT. K. A. McCracken*, S. I. Harik*, and J. C. LaManna. Univ. Hospitals and Case Western Reserve Univ. Med. Sch., Cleveland, OH 44106

There are regional differences in carrier-mediated glucose extraction in awake rats, possibly due to regional variations in capillary perfusion patterns. This possibility was explored by assessing regional glucose transport under anesthesia which reduces regional differences in blood flow and metabolism. In the awake rat, blood flow values were: cerebral cortex (Cx), 158; hippocampus (Hc), 107; and cerebellum (Cb), 82 ml/100g/min. Glucose extraction fraction (E) depended on plasma glucose concentration but was about twice as high in Cb than Cx or Hc. Glucose transport maxima (Tmax) values were: Cx, 269; Hc, 204; and Cb, 286 umol/100g/min. Under anesthesia (chloral hydrate, 400 mg/kg) blood flow to all regions was about 120 ml/100g/min; E was similar in Cx and Cb, but was distinctly less in Hc; and Tmax values were: Cx, 243; Hc, 164; Cb, 229 umol/100g/min. Chloral hydrate decreased Tmax in all brain regions despite increased blood flow to Cb and Hc and decreased blood flow to Cx. These results suggest that the differences in glucose transport between Cx and Cb in the awake rat are due to blood flow. However, differences in glucose transport between Hc and other regions are due to factors other than blood flow. Supported by NS 18150 and by the Cleveland Foundation.

47.1

EFFECTS OF INDOMETHACIN (INDO) AND SULINDAC (SUL) ON BASAL AND EXERCISE STIMULATED PGE_2 AND $PGF_{2\alpha}$ EXCRETION IN WOMEN. Edward J. Zambraski, Robert Dodelson*, Sandra M. Guidotti*, and Carol A. Harnett*, Rutgers Univ., New Brunswick, NJ 08903

To determine possible differences between INDO and SUL on basal and exercise induced changes in PG excretion, 6 women were tested under separate control (CON), INDO, and SUL treatment conditions. Both pre- and post-exercise (30 minute treadmill run at 70% max VO_2) renal PG excretion was evaluated after 3 days of INDO (150 mg/day), SUL (300 mg/day) or placebo. Values represent mean ± SEM.

	PGE (pg/min)		$PGF_{2\alpha}$ (pg/min)	
	Pre-Exer	Post-Exer	Pre-Exer	Post-Exer
Placebo	93±28	97±40	988±292	312±126
INDO	57±11	31±14	188±78	131±33
SUL	104±45	96±46	376±183	181±137

Urinary PGE_2 and $PGF_{2\alpha}$ responses to exercise were extremely variable, increasing only in 50% of the subjects under CON and SUL conditions but not with INDO treatment. PG inhibition did not alter exercise heart rate, VO_2 or rectal temperature. These data suggest there are differences between INDO and SUL in terms of basal and exercise induced changes in renal PG synthesis.

47.2

THE THYROTOXIC MINISWINE: EVIDENCE OF DIRECT MYOCARDIAL AND PERIPHERAL EFFECTS. H. Kirk Hammond*, Francis C. White*, M. Dan McKirnan*, Brian Guth, Sheila Flynn*, and John C. Longhurst. University of California, San Diego, La Jolla, CA 92093

The objective of this study was to see if the Yucatan miniswine was suitable for the study of the direct myocardial and peripheral effects of thyroid hormone. Resting oxygen consumption ($\dot{V}O_2$), measured by open circuit technique, was used as a correlate of the peripheral effects of thyroid hormone. Heart rate following autonomic blockade with atropine (0.075 mg/kg, iv) and propranolol (0.2 mg/kg, iv) was used as a correlate of the direct myocardial effects of thyroid hormone. Three animals were tested before and after 7 days of triiodothyronine (T_3; 1/mg/kg/day, iv). Supine resting $\dot{V}O_2$ changed from 7.4±0.2 to 13.2±0.4 ml/kg/min (mean±SD; p<.005). Intrinsic heart rate changed from 146±24 to 202±11 beats/min (mean±SD; p<.025). Dose-response curves to isoproterenol were not altered after 7 days of T_3 administration. Autopsy evidence in one animal showed a 26% increase in the left ventricle to body weight ratio compared to historical age-matched controls. These preliminary data suggest that the miniswine may be a suitable animal for further studies which delineate peripheral and direct myocardial effects of thyroid hormone and establish the relationship between myocardial blood flow and cardiac performance in thyrotoxicosis. (Supported in part by NIH HL 30222)

47.3

EFFECTS OF CHRONIC DOBUTAMINE ADMINISTRATION OF THE RESPONSE TO EXERCISE IN DOGS. M. Dan McKirnan*, Charles L. Stebbins*, H. Kirk Hammond*, Colin M. Bloor and John C. Longhurst. University of California, San Diego, La Jolla, CA 92093

Chronic dobutamine administration has been reported to improve exercise capacity despite its modest cardiovascular effect. To further evaluate this effect, 4 dogs were instrumented for measurement of blood pressure, indicator dilution cardiac outputs and Fick oxygen consumptions. Subsequently, submaximal and maximal treadmill exercise tests were administered before and after infusion of dobutamine 40µg/kg/min, 2 hrs/day, 5 days/wk, 3-6 weeks). Initially dobutamine increased heart rate (102±9 vs. 185±14 bpm, mean±SD), cardiac output (4.4±.5 vs. 8.7±1.1 L/min) and oxygen consumption (7.7±1.1 vs. 13.7±3.9 ml/min/kg)(all p<.05). Heart rate responses to submaximal exercise before and after 3 weeks of dobutamine infusion were not significantly different:

	Rest	4mph/6%	4mph/12%	4mph/16%	4mph/20%
Pre	120±17	190±21	207±18	218±15	231±13
3 Wks	101±13	171±14	192±12	206±10	222±12

After 6 weeks, submaximal heart rates in 1 dog decreased 6-19 bpm, but maximal oxygen consumption and heart rate were unchanged (119 vs. 123 ml/min/kg, 304 vs. 300 bpm, pre vs. post). These data suggest that reductions in submaximal heart rates, particularly at lower workloads, results from habituation to treadmill running and daily handling rather than a time-related improvement in exercise capacity resulting from dobutamine infusion. (Supported in part by NIH HL 30222)

47.4

GLUCOREGULATION DURING EXERCISE WITH ANEMIA. D.H. Wasserman*, H.L.A. Lickley*and M. Vranic. Dep't. of Physiol., University of Toronto, Toronto, Ontario, M5S 1A8.

While effects of anemia on the cardiovascular system have been studied extensively, little is known about its effects on metabolism. We wished to determine the effect of a 25% hematocrit reduction on glucoregulatory hormones and glucose fluxes during exercise in dogs. In 5 anemic dogs plasma glucose fell by 31 mg/dl and in 5 controls by 7 mg/dl at 90 min of exercise (p<.005). This exaggerated drop in plasma glucose occurred despite a larger increase in hepatic glucose production (Ra, Δ15.1 ±3.4 and Δ5.2±1.3mg/kg-min, p<.005) and was related to an exaggerated increase in glucose metabolic clearance (MCR, Δ24.6± 8.8 and Δ6.5±1.3ml/kg-min, p<.001). Exercise with anemia, in relation to controls, resulted in elevated levels of glucagon (1283±507 vs 514±99pg/ml, p<.05), norepinephrine (Δ1592±280 vs 590±155pg/ml, p<.0001), epinephrine (Δ2293±994 vs 385±186pg/ml, p<.005), cortisol (11.1±2.2 vs 6.2±1.0ug/dl) and lactate (Δ12.2 ±2.2 vs Δ4.2±1.8mg/dl, p<.0001). Insulin and FFA's were similar in both groups. In normal dogs, the glucagon/insulin ratio was the strongest correlate to Ra (r=.76). Although there was no significant correlation of norepinephrine to Ra in controls (r=.08), it was the best correlate to Ra in anemics (r=.60). In conclusion, exercise with a 25% hematocrit reduction results in 1) elevated lactate, norepinephrine, epinephrine, cortisol and glucagon levels; 2) an increased Ra which is likely related to the increased adrenergic drive; and 3) we speculate a near 4-fold increase in MCR is related to tissue hypoxia.

47.5

RELATIVE COST AND EFFICIENCY OF EXERCISE DURING HEAD-OUT IMMERSION. T.J. Doubt, M.P. Mullen*, B.L. Hart*, E.T. Flynn*. Naval Medical Research Institute, Bethesda, MD 20814.

Relative cost and efficiency of submaximal exercise in the dry and during head-out immersion (water temp.= 32 °C) were examined in 15 subjects breathing air. Bicycle workloads in the dry were 1 and 2 watt/kg. Immersion workloads were set to produce exercise $\dot{V}O_2$ that corresponded to dry exercise, requiring a decrease in bike workload settings. Each work period lasted 6 min (pedaling rate of 60 rpm). Work $\dot{V}O_2$ was the difference between exercise and resting $\dot{V}O_2$. Cost of exercise, obtained by linear regression of work $\dot{V}O_2$ vs. bike workload, revealed an increase in the intercept during immersion (-0.141 ± .082 L O_2/min in dry, 0.575 ± .098 in wet, p < 0.01). However, the slope of the relationship decreased during immersion (0.013 ± .001 L O_2 per min/watt in dry, 0.010 ± .001 in wet, p < 0.02). The reciprocal of slope, efficiency, thus increased during immersion (79 ± 4 watt-min/L O_2 in dry, 128 ± 21 in wet, p < 0.05). Similar changes in cost and efficiency were obtained while subjects breathed either normoxic He or 100% O_2. These findings indicate that immersion raises the cost and lowers the efficiency of submaximal leg exercise, probably through resistance effects on leg movement. However, relative cost decreases and efficiency increases during immersion as the submaximal workload increases. (Supported by NMRDC work units M0099PN.01A.0004 and M0099PN.01A.0007.)

47.6

THE EFFECTS OF EXERCISE ON REPRODUCTIVE ORGAN BLOOD FLOW IN FEMALE RATS. C.D. Kauer* and R.T. Dowell. Dept. of Physiology, Univ. of Kansas Medical Center, Kansas City, Kansas 66103

Measurements were made in nonpregnant (NP) and in day 6 pregnant (D6) rats. Sprague-Dawley rats were assigned to 4 exercise groups: TNP (n=6) and TD6 (n=6) groups ran 8 wks for 1 hr/day at 8.5 m/min, 0° incline; CNP (n=8) and CD6 (n=7) groups ran 5 min on alternate days. On the afternoon of proestrus/estrus, or day 6 of pregnancy, microspheres were used to measure blood flow (BF) at rest, 30 min elapsed exercise (EXER), and 5 min after exercise (POST). Mean BF ± SEM (ml/min/100g); P<.05: a vs rest; b between groups, are:

	OVARY			UTERUS		
GROUP	REST	EXER	POST	REST	EXER	POST
CNP	446±64	444±69	497±67	99±12	76±9	74±11a
TNP	398±96	293±80	245±59b	108±27	60±14a	50±10a
CD6	582±133	401±46	481±102	88±12	90±12	119±32
TD6	646±139	671±94b	1326±414b	84±8	95±19	107±17a

Rest BF was similar in T groups and their appropriate controls. NP uterine BF decreased during EXER remaining below REST at POST. No decrease in ovarian (all groups) or D6 uterine BF occurred. Estrus cycle length was the same in CNP and TNP. CD6 implantation site (IMP) BF (110±18) was similar to TD6 (130±12). TD6 IMP wt was lighter than CD6 (18.9±7 vs 22.1±1.8 mg, b). Lighter TD6 IMP wt suggests delayed implantation. Moderate exercise training in rats has no effect on estrus cycle length but may delay implantation (mechanism unknown). (Supported by grants HL28456 & HD16247).

47.7

MYOCARDIAL ISCHEMIA DURING EXERCISE IN NORMAL HEARTS

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Transient myocardial ischemia (TI) of the posterior left ventricular wall at rest in conscious dogs results in a slight increase in heart rate. TI during submaximal exercise has not been studied nor has the role of the left stellate ganglion (LSG) been investigated under these conditions. Five mongrel dogs were instrumented to measure arterial pressure (AP), left circumflex coronary flow velocity (LCV), heart rate (HR), and myocardial segment length. The dogs were run on a motor driven treadmill before and 10 days after the removal of the LSG. The LC was occluded with a hydraulic occluder for 1 min during exercise at 6.4 kph/16% grade. The results before, 30 sec and 60 sec after TI were:

	Control			LSG Removal		
	HR	AP	LCV	HR	AP	LCV
6.4/16%	215±10	112±12	43±6	221±6	108±10	38±5
30 Sec TI	230±9*	96±6*	0	243±3*	100±10	0
60 Sec TI	212±13	100±14	0	228±10	99±10	0

*P >.05 compared to 6.4 kph/16%

TI during exercise resulted in an increased HR that returned to pre-TI levels by 1 min. The increased HR during TI was not abolished by removal of the LSG and may be a result of a decreased AP. The increased heart rate during TI plus exercise may increase the potential for arrhythmias. (Supported by NIH 22154).

47.8

AEROBIC REQUIREMENTS OF OVERGROUND VERSUS TREADMILL RUNNING.

David R. Bassett Jr.*, Michael D. Giese*, Francis J. Nagle, Ann Ward*, Diane M. Raab*, Bruno Balke*. University of Wisconsin, Madison, WI 53706.

There is general agreement that the oxygen cost of level running is similar for both the treadmill (TM) and overground situations. However, controversy exists with regard to inclined running. The prevailing view, represented by the American College of Sports Medicine (ACSM) prediction formulas, is that overground hill running is theoretically more costly than inclined treadmill running. This study was designed to investigate the problem from an empirical standpoint. Seven male subjects performed overground and TM running at 2 grades and several different speeds (136-284 m/min). For the outdoor trials, subjects covered a distance of 950 m at a constant pace, and expired gas was collected over the last 150 m. Matching trials were then performed on the treadmill at the same speed and % grade. Regression lines were calculated for speed vs. oxygen consumption ($\dot{V}O_2$). At both the 0 and 5.7% grades, no significant difference was observed between overground and TM running ($P > .05$). The empirical observations fit the ACSM prediction formulas for level running and inclined TM running only. The ACSM prediction formula for overground hill running over-predicted $\dot{V}O_2$. In light of these findings, the prediction formulas were reevaluated and an alternative explanation of the vertical component of VO_2 for hill running is proposed.

47.9

RELATION OF BLOOD LACTATE CHANGES IN ACTIVE AND INACTIVE HINDLIMB DURING A PROGRESSIVE ISOTONIC EXERCISE.

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Alterations in venous [lactate] were studied in eight animals anesthetized with urethane and chloralose after cannulae were placed in both femoral veins. Stimulation of the distal stump of the cut sciatic nerve at 1 Hz was used to induce plantar flexions of the right hindlimb which lifted loads comparable to 2,5,8,30 or 50% of an afterload at which only an isometric tension developed. Each session consisted of a series of 6-min exercise periods interspersed among 5-min nonexercise periods, and a 10-min postexercise period. Free-flowing venous blood samples were obtained simultaneously from both cannulae just before the first exercise period, during the last min of each of the 5 exercise periods, and 10-min after the last exercise period. A progressive increase in [lactate] occurred in both limbs, being detected earlier in active limb. However, correlations of changes in [lactate] in both limbs varied widely among individual animals, ranging from -0.05 to 0.98. Further, a minimum increase in [lactate] in active limb seemed necessary for its appearance in the other limb. Thus, an increased [lactate] in a sampling site remote from active limb may reflect the point at which systems designed to minimize changes in plasma [lactate] become saturated more accurately than it signals the onset of anaerobic metabolism. (Sponsored by RR05388).

47.10

INJURY TO SKELETAL MUSCLES OF MICE BY ECCENTRIC CONTRACTIONS

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Our purposes were to test the hypothesis that eccentric contractions result in greater injury to skeletal muscle fibers than isometric or concentric contractions and to determine the extent of exercise-induced injury and the time course of recovery. The mice were anesthetized. The leg was secured firmly and maintained at 37°C. The distal tendon of the extensor digitorum longus muscle was isolated and attached to an ergometer. The peroneal nerve was stimulated for three 5 min periods at 150Hz, with a train duration of 300ms every 2s. For eccentric and concentric contractions the muscle was stretched or released 20% of optimal fiber length at 6mm/s during the last 200ms of each contraction. After stimulation the distal tendon was reattached and incisions closed. The muscles were removed after 1 to 30d and maximum isometric tension(Po) was measured in vitro at 37°C. Muscle sections were stained for hematoxylin and eosin. Isometric, concentric, and sham operated muscles showed no histologic evidence of injury and Po was 80% of control at 3d and 7d. The Po(as % of control) of muscles after eccentric contractions was 22±3% at 3d, 28±2% at 7d, and 84±3% at 30d. Muscle degeneration was evidenced at 3d. Muscle regeneration, which was seen at 4d, was complete by 30d. We conclude that with our protocol, eccentric, but not isometric or concentric contractions, cause significant muscle fiber degeneration and regeneration. (USPHS NS17017).

PULMONARY GAS EXCHANGE AND VENTILATION

48.1

$\dot{V}_A/\dot{Q}$ INEQUALITY AND DIFFUSION LIMITATION IN NORMAL SUBJECTS EXERCISING AT SEA LEVEL.

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We previously found evidence suggestive of $\dot{V}_A/\dot{Q}$ relationships worsening with exercise in 9 normal subjects at sea level. In addition, in the 3 subjects capable of VO_2 >3 L/min, arterial PO_2 at such $\dot{V}O_2$ was lower than predicted from simultaneously measured inert gas elimination data, suggesting alveolar-endcapillary O_2 diffusion limitation. To better assess both of these findings, we performed similar steady state exercise measurements of inert and respiratory gas exchange in a further 8 normal subjects with generally higher exercise capacity. Data from the two studies were combined after showing that there were no statistically significant differences between them. With the larger subject population, logSD of the perfusion distribution increased with exercise by 0.05 per litre $\dot{V}O_2$ ($P=.02$). Other indices also reflected the increase in $\dot{V}_A/\dot{Q}$ inequality with exercise. Breathing 100% O_2 did not abolish the increased $\dot{V}_A/\dot{Q}$ mismatch. The difference between measured and predicted alveolar-arterial PO_2 differences became significant at $\dot{V}O_2$ 2.7 L/min (10.4 torr mean) and increased progressively with exercise reaching 21 torr at $\dot{V}O_2$ =4.0 L/Min ($P<.01$). These results confirm: 1) the previous suggestion that sea level exercise in normal subjects increases $\dot{V}_A/\dot{Q}$ inequality, and 2) at $\dot{V}O_2$ of about 3 L/min and above, alveolar-endcapillary diffusion limitation is detectable.

48.2

PULMONARY ARTERY PRESSURE AND WORSENING $\dot{V}_A/\dot{Q}$ RELATIONSHIPS DURING EXERCISE IN NORMAL MAN.

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We previously found an increase in $\dot{V}_A/\dot{Q}$ mismatching with exercise in normal subjects. This was more marked at altitude than sea level, and at altitude 100% O_2 breathing abolished this increase, suggesting that hypoxic vasoconstriction may play a role in worsening $\dot{V}_A/\dot{Q}$ relationships. To further address this issue, we repeated our earlier studies, this time including direct pulmonary artery pressure measurements. $\dot{V}_A/\dot{Q}$ inequality again increased with exercise at altitude and was ameliorated by breathing 100% O_2. A single tight relationship was found between mean pulmonary artery pressure ($\overline{PPA}$) and $\dot{V}_A/\dot{Q}$ dispersion over all rest and exercise levels ($\dot{V}O_2$ 0.3 - 4.0 L/min), all altitudes (sea level, 10,000 ft. (PB 523) and 15,000 ft. (PB 429)) and FIO_2 (ambient air or 100% O_2 at each altitude). Mean logSD of the perfusion distribution increased from about 0.35 at $\overline{PPA}$ of 15 torr to about 0.55 at $\overline{PPA}$ of 40 torr. However, minute ventilation was also found to correlate with dispersion, so that the current study cannot exclude either airway or vascular factors as causes of the increased $\dot{V}_A/\dot{Q}$ inequality. Further work is necessary to separately study distribution of ventilation and/or blood flow to clarify the mechanisms of increased $\dot{V}_A/\dot{Q}$ dispersion on exercise.

48.3

CARDIOVASCULAR RESPONSE TO INHALED AND INTRAPERITONEALLY INFUSED CARBON MONOXIDE IN THE DOG G. Gutierrez, H. Rotman, D. Dantzker. (Div Pulm Med) Univ of Texas Med School at Houston and Univ of Michigan Med School.

We compared the hemodynamic and blood gas data from anesthetized dogs given 0.15% CO to breathe (INH group), and from dogs injected with 100% CO intraperitoneally while breathing room air (ITP group). The animals were observed for a period of 150 minutes after reaching a level of 50% HbCO. The time required to reach this level was similar for both groups, i.e., 102±54 minutes and 90±21 minutes for the ITP and INH groups respectively. The average HbCO% for the duration of the experiment was 58.3±2.4% and 62.9±1.5% for the ITP and INH groups respectively. All the animals survived in each group. There was no significant difference in their hemodynamic response to CO except for a higher mean systemic blood pressure in the INH group. This difference was also present during the baseline measurements suggesting that it was not related to the effects of CO. After the 150 minute comparison period, we attempted to precipitate a terminal cardiovascular crisis by increasing the amount of CO given. The animals in the ITP group lived indefinitely, since the measured HbCO% level did not rise above 70% regardless of the amount of CO injected. Those in the inhalation group died with an average HbCO% of 80.0±3.5%. It is concluded that the toxic effect of CO is the result of impaired oxygen delivery to the peripheral tissues. No evidence was found that different routes of administration grossly alter the physiological response to carbon monoxide.

48.4

INTERACTION OF PEROXYACETYL NITRATE AND OZONE ON PULMONARY FUNCTIONS. D.M. Drechsler-Parks*, J.F. Bedi* and S.M. Horvath. Inst. of Environ. Stress, U. of CA, Santa Barbara, CA 93106.

The metabolic and pulmonary function effects were investigated in 10 non-smoking, young adult males who were exposed for 2 hours (20°C WBGT) to four conditions: (1) filtered air (FA), (2) 0.30 ppm peroxyacetyl nitrate (PAN), (3) 0.45 ppm ozone (0_3), and (4) 0.45 ppm 0_3 + 0.30 ppm PAN (PAN/0_3). The subjects alternated 15 minute periods of rest and 20 minute periods of bicycle ergometer exercise at a work load requiring a $\dot{V}_E$ of 27 L/min (BTPS). Functional residual capacity (FRC) was determined pre- and post-exposure. Forced vital capacity (FVC) was determined before and after exposure, and 5 minutes after each exercise period. Heart rate was monitored throughout the exposure, and ventilatory minute volume ($\dot{V}_E$), oxygen uptake ($\dot{V}_{O_2}$), respiratory rate (f_R), and tidal volume (V_T) were measured during the last 2 minutes of each exercise period. There were no changes in any variable consequent to FA or PAN exposure. The only metabolic changes due to 0_3 and PAN/0_3 exposure were a decrease in V_T and a concomitant increase in f_R, with no change in $\dot{V}_E$. Both 0_3 and PAN/0_3 induced significant ($P<0.05$) decrements in FVC, $FEV_{1.0}$, $FEV_{2.0}$, $FEV_{3.0}$, $FEF_{25-75\%}$, IC, ERV, and TLC. The decrements following PAN/0_3 exposure averaged 10% greater than those following 0_3 exposure. The results suggest an interactive effect between PAN and 0_3, possibly explained by total oxidant load. (Supported by Calif. Air Resources Board Grant #A1-069-32).

48.5

COMPARATIVE LUNG SOUND ORIGINS: ADULTS, TERM INFANTS AND PREMATURE INFANTS. S. S. Kraman and J. F. Kanga *. V.A. Medical Center, and Univ. of Kentucky, Lexington, KY 40536

Vesicular lung sounds are presumed to originate in larger airways where turbulent airflow exists. Several investigators have failed to find a source above the main carina and others have demonstrated that the sound is a regional phenomenon. Nonetheless, the precise sites have never been demonstrated. Because it is easy to identify sound production in the trachea, we studied the sounds of healthy adults, term (mean weight 3.5 Kg) and premature newborn infants (mean weight 1.38 Kg) to see whether, in these small lungs and airways, the source of sound would be detectable in the trachea. We placed microphones on the chest wall over the base of each lung and used coherence analysis as a means of detecting central (tracheal) sound production. For the adults, no central airway component could be identified. For the term infants, a coherence peak of 0.69 occurred at 350 Hz. For the premature infants, a broader coherence peak of 0.72 at 350 Hz was noted as well as a suggestion of increased coherence at higher frequencies. This confirms the absence of a tracheal source of lung sound in adults and demonstrates such a source in infants The diameter of the trachea of the newborn infant, and the airflow within it, are similar to those of the adult segmental bronchus. Our data, therefore, suggest that the source of the lung sound heard on the chest in adults originates in the vicinity of the segmental airways.

48.6

COMPARISON OF LUNG SOUND FREQUENCY SPECTRA OF NEWBORN INFANTS AND ADULTS. J. F. Kanga * and S. S. Kraman. V.A. Medical Center and Univ. of Kentucky. Lexington. KY 40536

Auscultation of the new born infant chest reveals lung sounds that are different to the ear from those of adults. To characterize this subjective difference, we compared the lung sounds of 10 full term infants with those of 8 adults. Both groups were free of cardio-respiratory disease and the adults were non-smokers. Lung sounds were recorded from locations over the right and left upper and lower lobes during the middle of inspiration, using miniature, air coupled microphones fastened to the skin with tape rings. Frequency analysis was by fast fourier transform (FFT). We averaged the spectra derived from two breaths at each of the four locations from all subjects in each group. All subjects were studied using the same procedures and equipment so that observed differences in frequency could not be attributed to variation in technique. Our analyses revealed that, at all four locations, the spectral components of the infant's lung sounds above 300-400 Hz were greater in amplitude than the adult's. Below 300-400 Hz, the lower frequencies of the adults predominated. The differences were statistically significant at all four locations. These findings support the impression that the lung sounds of infants contain more high frequency components than those of adults. The reasons for this are probably that, in infants, the filtering properties of the lung are different from those of the adult lung, and that the sound traverses less lung tissue between the generating airways and the chest wall.

48.7

THE EFFECT OF CARRIER GAS DENSITY ON GAS TRANSPORT DURING HIGH FREQUENCY OSCILLATION. E.J. McCarthy*, D. Kerem and J. Clarke. Department of Physiology, Uniformed Services University, and Naval Medical Research Institute, Bethesda, Maryland 20814

We sought to determine the effect of carrier gas density on gas transport with both high frequency oscillation and conventional ventilation. Anesthetized intubated dogs (7.7-15 kg) were ventilated by either conventional ventilation (Harvard ventilator) or by high frequency oscillation (Emerson piston pump, 20 ml stroke volume, 30 Hz) using two gas mixtures (80% He/20% 0_2, 80% SF_6/20% 0_2). With high frequency oscillation, the gases were delivered at constant bias flow. By shunting various fractions of the ventilator output, chest wall motion measured by accelerometers was maintained constant during gas density changes. With conventional ventilation, P_aCO_2 and P_aO_2 did not change with gas density. However, with high frequency oscillation P_aCO_2 and P_aO_2 showed a significant difference at $p<.05$ (P_aCO_2[He] = 38.1 ± 2.7 torr, $P_aCO_2(SF_6)$ = 30.6 ± 2.0, P_aO_2[He] = 70.3 ± 6.2, $P_aO_2(SF_6)$ = 89.8 ± 6.4). These results show that gas density affects gas exchange with high frequency oscillation but not with conventional ventilation. Furthermore, gas exchange improves with increased carrier gas density during high frequency oscillation. This work supports the models of Kurzweg and Jaeger (Phys. Fluids, in press) and Epstein (Fed. Proc., 43:322). (Supported in part by NMRDC Work Unit M009PN.01B.009.)

48.8

THE USE OF PEEP WITH HIGH FREQUENCY JET VENTILATION FOLLOWING SURFACTANT DISPLACEMENT IN DOGS. Kathleen M. Beney*, Gary F. Nieman, Michael S. Jastremski*, Carl E. Bredenberg, Upstate Medical Center, Departments of Critical Care Medicine and Surgery, Syracuse, New York 13210.

Previous studies in our lab have shown that High Frequency Jet Ventilation (HFJV) is unable to provide adequate oxygenation following surfactant displacement, due to insufficient peak inspiratory pressures (PIP). This study examined the effects of adding PEEP to HFJV in order to improve oxygenation in the same surfactant depleted non-compliant lung model. Catheters were placed in 7 intubated, anesthetized mongrel dogs for measurement of systemic and pulmonary pressures, blood gases and cardiac output (CO) by thermodilution. Airway pressure was measured through the pressure monitoring port of a Hi-Lo Jet endotracheal tube; static compliance and venous admixture were calculated. Following control measurements, surfactant was displaced with 15mg/Kg of the aerosolized detergent dioctyl sodium sulfosuccinate (OT) in a vehicle of 50% ETOH and 50% saline. PEEP of 10cm H_2O was added immediately post OT. PaO_2 fell dramatically following OT (105±32 to 41±3.9 mmHg, $P<0.05$) and did not improve significantly in 2 hours. PIP increased to levels similar to those of conventional ventilation without PEEP (41±1.5 to 13±3.6 mmHg, $p<0.05$). CO fell progressively throughout the experiment (Baseline= 3.2±0.6 to 2.8±1.9, 2 hours post OT). These data demonstrate that the use of PEEP with HFJV was unable to provide adequate oxygenation despite the increase in PIP.

48.9

PHASE DIFFERENCES BETWEEN TRACHEAL WALL AND RESPIRATORY IMPEDANCE SUGGEST THAT AXIAL PENDELLUFT OCCURS BETWEEN AIRWAY WALLS AND LUNG DURING HFO. M.I. Kotlikoff*, A.C. Jackson, J.P. Butler*, J.D. Berry*, and J.R. Gillespie. Dept. Physio. Sci., U.C.D., Davis, CA 95616.

Recent observations of central airway wall expansion during high frequency oscillation (HFO) indicate that the volume of central airway expansion becomes a considerable fraction of the delivered tidal volume (Vt), especially at high frequencies. It has been suggested that this central airway expansion results in shunting of Vt away from gas exchange areas of the lung, thus reducing the efficacy of HFO. We measured tracheal wall and respiratory system impedances from 2-96 Hz in anesthetized, paralyzed dogs and from these measurements computed the magnitude as well as the phase relationship between tracheal wall flow ($\dot{V}wall$) and axial flow into the respiratory system ($\dot{V}lung$). We found that the magnitude of $\dot{V}wall/\dot{V}lung$ was large at higher frequencies; at frequencies above 10 Hz, however, a component of $\dot{V}wall$ was 180° out of phase with $\dot{V}lung$, which represents axial pendelluft between the airway wall and lung compartments. The out of phase component increased with frequency to a value of 20% of $\dot{V}lung$ at 40 Hz, and 53% at 96 Hz. We suggest that, although airway wall motion during HFO appears to be of considerable magnitude, the phase relationship is such that wall motion may in fact contribute to axial gas mixing, thus improving gas exchange during HFO. (Supported by NIH HL-32331, and US-NIEHS Grant ES00628)

48.10

ALVEOLAR COLLAPSE FROM MECONIUM LIPID ASPIRATION. David A. Clark*, Gary F. Nieman, Jeffrey E. Thompson*, John E. Rokahr*, Andy M. Paskanik* and Carl E. Bredenberg. Depts. of Pediatrics and Surgery, Upstate Med. Ctr., Syracuse, NY. 13210

We have previously demonstrated that meconium free fatty acids (FFA) alter surface tension in vitro. We examined the role of the meconium FFA (palmitic, stearic, and oleic) on alveolar collapse in 4 mongrel dogs who were anesthetized, placed on a piston ventilator and subjected to a left thoracotomy. Cardiac output, blood gases, femoral, pulmonary and left atrial pressures were measured and static lung compliance was calculated. 50 mg of a FFA normal saline suspension of purified palmitic, stearic and oleic acids (2:1:1 ratio, simulating their proportions in meconium) was lavaged into the lungs, and the animals were monitored for 2 hours. PaO_2 decreased from 89.9 6.5 TORR to 68.8 4.1 TORR at 15 minutes, stabilizing at 73.6 7.0 TORR by 2 hours. There was no change in pH, $PaCO_2$, or any hemodynamic parameter. Following a second lavage with 500 mg of the FFA normal saline suspension, PaO_2 worsened to 57.6 14.9 TORR, $PaCO_2$ increased and pH decreased proportionately. The animals were then sacrificed and a portion of lung was minced in saline and the surface tension was measured in a Wilhelmy balance. Although atelectasis and plentiful airway foam were seen, the surface tension minimum of lung extract and airway foam was less than 10 dynes/cm. We conclude that the free fatty acids in meconium may lead to alveolar collapse by displacing surfactant from the alveolus.

48.11

THE ROLE OF MECONIUM LIPIDS (FREE FATTY ACIDS) IN MECONIUM ASPIRATION. David T. Terasaka*, David A. Clark*, Gary F. Nieman, Babhuti N. Singh*, Jeffrey E. Thompson* and John E. Rokahr*. Depts. of Pediatrics, Biochemistry and Surgery, Upstate Medical Center, Syracuse, New York 13210.

Continuous positive airway pressure has been reported to be of benefit early in the course of neonatal meconium aspiration, which suggests that it is stabilizing alveoli whose surfactant may be displaced. We examined the lipid fraction of 18 fresh human meconiums and analyzed their surface tension properties in a Wilhelmy balance. The lipids were extracted in ethanol-chloroform and petroleum ether, separated by thin layer chromatography, and characterized by gas liquid chromatography. The primary surface active lipids were the free fatty acids found in an aggregate concentration of approximately 1 mg/gr of meconium. Although there was wide variability, the predominant free fatty acids were palmitic, stearic and oleic found in an approximate 2:1:1 ratio. The surface tension minimum of these compounds alone was not lower than 20 dynes/cm. When added to dog lung extract the surface tension minimum of surfactant was eliminated and approximated that of the meconium free fatty acids. These data suggest that the free fatty acids of meconium may disrupt the surface tension minimum induced by alveolar surfactant leading to alveolar collapse.

48.12

PULMONARY TISSUE VOLUME IN SMOKERS Marcy F. Petrini, Thomas A. Walker * and Margaret S. Phillips *. Univ. of Miss. Med. Ctr., Jackson, Ms 39216

We measured pulmonary tissue volume (V_t) by rebreathing acetylene in male smokers who were divided into 3 groups: 1) light smokers, ≤ 20 pack years; 2) moderate smokers, >20≤40 pack years; and 3) heavy smokers, >40 pack years. In light and moderate smokers, V_t was within normal limits (mean 106% of predicted) when compared to V_t from a male non-smoking population of the same age group; this was true whether body surface area or vital capacity was used to predict V_t. In heavy smokers results were varied but were dependent on the time for the insoluble gas to complete mixing (MT) during rebreathing as shown below:

n	V_t % predicted	MT, breaths
3	106	≤ 3
2	88	4
4	68	5
1	26	> 5

where n is the number of subjects. Thus we conclude that the insoluble gas during rebreathing can be used to estimate whether the measured V_t is a reliable estimate of true tissue volume. (Supp by NIH Grant HL26051 and a Mississippi Lung Association Grant-in-Aid of Research)

RENAL TUBULE TRANSPORT AND ADH

49.1

TOXICITY OF MONENSIN SODIUM IN DOMESTIC PONIES: A POSSIBLE NEW MODEL FOR FANCONI SYNDROME? James F. Amend. University of Nebraska-Lincoln, Lincoln, NE 68583 - 0905

The Fanconi syndrome (de Toni-Debre'-Fanconi syndrome) is a generalized resorptive defect of the proximal renal tubule, with associated wasting of amino acids, glucose, bicarbonate, phosphate, and uric acid. This condition has been modeled in laboratory animals using maleic acid to disturb function of proximal tubules. We have studied a group of domestic ponies exposed to the carboxylic ionophore monensin sodium (M), in an effort to determine its mode of toxicity in this species. M is commercially used as a cattle feed additive which increases feed efficiency, but is potentially lethally toxic to horses ingesting it. Ponies were given oral doses of 3 mg/kg of M, and were monitored for a number of clinicopathologic variables. Sampling occurred at 4 hour intervals until toxic signs demanded that the animal be euthanatized for humane reasons. The results of serum and urine analyses showed that serum potassium, phosphorous, and glucose were progressively depressed as the toxic episode developed, while uric acid showed a variable but mild decline; clearance of potassium and phosphorous was increased. Urine output was elevated early in the period of toxicity. Amino acids and bicarbonate were not determined. Numerous solutes require obligatory sodium coupling for transport across the luminal membrane; M is sodium selective in its primary cation transport. (This study was supported in part by Eli Lilly and Co., and by resources of the Agricultural Research Division, IANR, University of Nebraska-Lincoln.)

49.2

RENAL HANDLING OF Tc-99m COMPLEXES OF HYDROXYDICARBOXYLIC ACIDS. Richard P. Spencer, Karen S. Kolstad*, Larry A. Spitznagle*, Nita K. Jain*, Dept. Nuclear Medicine, Univ. Connecticut Health Center, Farmington, CT 06032.

Dimercaptosuccinic acid (DMSA) forms a complex with Tc-99m (Sn) which accumulates in the kidneys. We probed analogues for binding Tc-99m(Sn) and renal uptake. Controls were malonic and succinic acids (C-3 & C-4 dicarboxylic acids), DMSA and a glomerular agent (DTPA). The compounds were HOOC.(C)x.(OH)y.COOH.

No.	C=x	OH=y		% Binding	Binding pH
1.	1	1	Monohydroxymalonic	95	4-5
2.	1	2	Dihydroxymalonic	95	4-5
3.	2	1	L-malic acid	82	5-6
4.	2	2	L-tartaric acid	93	3-4
5.	2unsat	2	Dihydroxyfumaric	95	5-6
6.	2	4	Tetrahydroxysuccinic	96	3-4

In mice, the complexes had renal accumulation. None bound as well as the Tc-99m-DMSA complex or had higher renal values at 1 hour than at 15 minutes. After DMSA, highest renal uptake was shown by dihydroxymalonic acid. Least renal activity was noted with the Tc-99m complex of dihydroxyfumaric acid (the unsaturated compound). This series of hydroxydicarboxylic acids allows insights as to structure-biological activity. (Supported by USPHS CA 17802, National Cancer Institute).

49.3

FACILITATED DIFFUSION OF METHYLSUCCINATE FROM INTERSTITIUM INTO RENAL PROXIMAL TUBULAR CELLS

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The contraluminal influx of methylsuccinate from interstitium into proximal tubular cells was measured by means of collapsed tubular lumina. The injected Ringer solution contained different concentrations of methylsuccinate and, additionally, inulin as an extracellular space marker. After contact times between one and ten seconds, the solution was withdrawn from the capillaries and the disappearance of methylsuccinate was measured.

It turned out that the conditions of transport and the experimental data are consistent with the predictions of a facilitated diffusion model. The calculations yield a Michaelis-Menten constant K_m equal to 0.12 mM and a contraluminal influx J_{max} equal to 0.50 pmol/s·cm (related to tubular length).

49.4

ACCUMULATION OF URIC ACID (UA) AND P-AMINOHIPPURIC ACID (PAH) IN KIDNEY TUBULES FROM GENETICALLY HYPERURICEMIC CHICKENS. Shiu-Ming Kuo* and Richard E. Austie* (SPON: R.H. Wasserman). Cornell Univ., Ithaca, NY 14853

Kidney tubules were isolated by collagenase treatment from two strains of 4-6 week old chicks selected genetically for hyperuricemia (HUA strain) or low plasma uric acid concentration (LUA strain). Substrate accumulation was measured during 5 minutes of incubation in Krebs-Henseleit buffer at pH 7.4. As the UA concentration in the medium increased from 0.01 mM to 0.5 mM, UA accumulation in LUA tubules increased from 4.6 to 181 pmole/min/mg dry weight. As PAH concentration increased from 0.01 mM to 0.5 mM, PAH accumulation in LUA tubules increased from 31 to 243 pmoles/min/mg. The maximum intracellular UA and PAH concentrations in LUA tubules were 1.9 and 6.8 fold, respectively, that of the medium. HUA tubules accumulated, on the average, only 18±5% and 31±4% as much UA and PAH, respectively, as LUA tubules. PAH at 0.8 mM depressed UA accumulation in LUA and HUA strains by 75% and 56%, respectively, even at 80-fold excess PAH. This represented the maximum inhibition of UA transport by PAH. Ouabain at 0.1 mM caused a 44% inhibition of UA and PAH accumulation in the LUA strain but caused 10% inhibition of UA and 30% inhibition of PAH transport in the HUA strain. The results indicate a defect of UA and PAH transport in HUA tubules, affecting mainly a ouabain-sensitive transport process. While UA and PAH may share transport systems, only part of the UA accumulation in chicken kidney tubules can be inhibited by PAH.

49.5

THE EFFECTS OF COLCHICINE ON RENAL BRUSH BORDER MEMBRANE (BBM) TRANSPORT OF PHOSPHATE (Pi). James S. Newman* (SPON: T.P. Dousa). Nephrology Research Unit, Mayo Clinic and Foundation, Rochester, MN 55905.

The present in vivo studies were performed to evaluate the possible role of cytoplasmic microtubules in cellular mechanism of Na^+-gradient-dependent transport of Pi across BBM. Studies were conducted on TPTX rats fed with diet containing 1.4% phosphate, with or without treatment with thyroid hormone (T_3) to enhance the BBM uptake of Pi. Animals were injected i.p. with colchicine (COL), lumicolchicine or vehicle alone, 20 hours prior to sacrifice and preparation of BBM. Administration of COL resulted in decreased Na^+-gradient-dependent BBM uptake of Pi, both in control rats (Δ-63%) and in rats treated with T_3 (Δ-48%), compared to controls. Na^+-gradient-dependent uptake of L-proline measured in the same BBM preparations was not affected by COL treatment. Administration of lumicolchicine, an inactive analog of COL, had no inhibitory effect on BBM uptake of Pi.

Conclusion: These experiments suggest, in an indirect way, that the integrity of cytoplasmic microtubules in cells of proximal convoluted tubules is required for luminal BBM uptake of Pi in both basal and T_3-stimulated state.

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49.6

EFFECT OF ACUTE GLUCOCORTICOID INFUSION ON NEPHRON PHOSPHATE TRANSPORT. S. K. Webster, A. Haramati, and F. G. Knox, Dept. of Physiol., Mayo Medical School, Rochester, MN 55905

Glucocorticoids restore the phosphaturic response to parathyroid hormone (PTH) in rats fed low phosphate diet (LPD). The present experiments determined the site of inhibition of phosphate reabsorption in rats fed LPD for 4 days. Micropuncture samples from superficial nephrons were obtained 2 hrs after acute TPTX, then 1 hr after initiation of Dexamethasone (DEX) infusion (0.4 mg/kg·hr), then again 1 hr following initiation of PTH infusion (1 u/kg·min after bolus of 33 u/kg) with continued DEX infusion.

	Fractional Delivery of Phosphate (%)		
	Late Proximal	Early Distal	Urine
Basal	7.1±2.1	2.2±0.6	0.3±0.2
DEX	14.4±3.5*	3.8±1.3	0.1±0.1
DEX + PTH	32.7±6.4*	5.6±1.9	5.9±2.6*

*$p<0.025$ as compared to samples from previous period

These results demonstrate that in rats fed LPD, DEX inhibits phosphate reabsorption in the superficial proximal tubule, which does not result in phosphaturia due to reabsorption in more distal segments of the nephron. In the presence of DEX, PTH further inhibits phosphate reabsorption in the proximal tubule. In addition, there is an increase in phosphate excretion due to inhibition of distal phosphate reabsorption.

(Supported by NIH AM07013)

49.7

MAGNESIUM BALANCES AND ^{28}Mg STUDIES IN MAN. Herta Spencer, Dace Osis,* and Clemontain Norris* V.A. Hospital, Hines, IL 60141

The magnesium status was determined in adult males by performing complete magnesium balances for several weeks during a constant dietary magnesium intake. The diet and urinary and fecal magnesium excretions were analyzed for magnesium. The intestinal absorption of magnesium was determined as net absorption of magnesium from magnesium balances and from 6-day cumulative fecal ^{28}Mg excretions following an oral dose of $^{28}MgCl_2$. Intravenous tracer doses of ^{28}Mg were given in order to use the double tracer technique for the intestinal absorption of magnesium and to determine the endogenous fecal magnesium excretion. ^{28}Mg plasma levels were determined serially after oral and intravenous ^{28}Mg. The absorption of magnesium determined by the double tracer technique, from fecal ^{28}Mg excretions and as net absorption agreed well, and averaged 47% of the dose. Magnesium balances and the absorption of magnesium did not change during different calcium intakes up to 2000 mg/day. The excretion of magnesium into the intestine, that is the endogenous fecal magnesium, was low and averaged 7% of the dose. The studies have shown that absorption of magnesium can be reliably determined by either of the three methods described above. In chronic renal failure, the intestinal absorption of magnesium was reduced to one third the normal value.

49.8

POST ISCHEMIC KIDNEY: SODIUM REABSORPTION, OXYGEN CONSUMPTION AND GAMMA GLUTAMYLTRANSFERASE EXCRETION. David Herminghuysen* and T.C. Welbourne. Dept. Physiology, LSUMC, Shreveport, LA. 71130.

The effect of 30 minutes of renal artery occlusion on Na^+ reabsorption, $\dot{V}\text{-}O_2$ and membrane integrity was evaluated over the immediate 1 hr reflow period. Rats, weighing 350-450 g, were anesthesized with inactin and prepared for clearance and renal extraction measurements. Glomerular filtration rate, GFR, as C-In and renal plasma flow, C-PAH/E-PAH, were determined over 4 consecutive 15 minute periods; renal venous samples were obtained via an indwelling catheter. Tubular Na^+ transport, T-Na^+, and $\dot{V}\text{-}O_2$ were measured in each period; excretion of GT was employed as an index of membrane integrity. In period (1) GFR, T-Na^+ and $\dot{V}\text{-}O_2$ were reduced ≈ 25% percent; T-Na^+/$\dot{V}\text{-}O_2$ remained unchanged from control. Excretion of GT increases from 67±9 to 1,085±128 nunits/min/ml GFR with 67% in the membranous form. In period (2) GFR and T-Na^+ return to ≈ 50% of control while T-Na^+/$\dot{V}\text{-}O_2$ decreases from control value of 23.9±2.0 to 16.1±2.5; GT excretion increases 55%, now largely in the soluble form. In period (3) T-Na^+/$\dot{V}\text{-}O_2$ drops to 8.9±1.0 and soluble GT excretion increases. In period (4) GT decreases and T-Na^+/$\dot{V}\text{-}O_2$ returns toward control, 18.6±1.9. A redistribution of O_2 dependent energy generation from T-Na^+ to cellular reparation may be reflected by the shift in the form of GT excretion.

49.9

THE EFFECT OF ADRENALECTOMY ON CHLORIDE TRANSPORT IN THE LOOP OF HENLE IN THE RAT. W. J. Welch*, C. E. Ott and T. A. Kotchen*. University of Kentucky, Lexington, KY 40503.

We have shown that plasma renin concentration (PRC) is elevated in adrenalectomized (Adx) rats, and does not fall following saline infusion. Adx rats have a reduced ability to dilute and concentrate urine. These observations are consistent with the hypothesis that reduced chloride transport in the loop of Henle increases renin release. This study directly measured chloride reabsorption in the loop of Henle of saline drinking Adx (n=7) and sham-operated (n=6) rats before and after saline infusion. One week after Adx or sham surgery animals were prepared for micropuncture. Three proximal and three distal tubules were marked and fluid was collected from each before and after saline infusion. Loop chloride reabsorption was calculated as the difference in proximal delivery and distal delivery. PRC of Adx rats was greater than sham before (315 ng AI/hr ± 55 to 60 ±6, p<.001) and did not change after infusion. PRC of sham was reduced following saline infusion (60 ± 6 to 25 ± 3, p<.01). Loop reabsorption of chloride in Adx rats was less than sham both before (683 pEq/min ± 102 to 1405 ± 296, p<.001) and after (1211 ± 168 to 2215 ± 180, p<.01) saline infusion. Distal chloride concentration was higher in Adx rats than sham rats after infusion (82 mEq/L ± 3 to 57 ± 9, p<.01). Change in hematocrit, plasma volume and blood pressure did not differ between groups. We conclude that an increase in renin release in Adx rats is associated with a reduction in loop transport of chloride.

49.10

EFFECT OF PAPILLARY MICROPUNCTURE THROUGH AN INTACT URETER ON OSMOLALITY AND UREA IN URINE AND PAPILLA. Dale Hartupee and John Passmore. Univ. Louisville, Louisville, KY 40292.

We previously reported that in hydropenia, papillary micropuncture through an intact ureter decreased urine osmolality and increased renal prostaglandin (PG) E_2 excretion. Meclofenamate (meclo) blocked these effects. The present studies were done to ascertain the effect of the PGs on urea and osmolality gradients across the papillary collecting duct. Osmolality (osm) and urea concentration (mEq/L) were measured in urine (U) and papillary interstitium (Pap) before and 30 min after papillary micropuncture through an intact ureter. Three groups of hydropenic rats were studied, an experimental group (micropuncture), a group given meclo (2 mg/kg hr) prior to the micropuncture, and a time control group. U_{osm} decreased after micropuncture in the experimental group (2026±22 to 909±184 mosm/kg) but was unchanged in the meclo (2042±181 to 1716±97) or time control groups (2069±86 to 2133±140). Values for U and Pap after micropuncture are:

Group	U_{osm}	$P_{ap}/_{osm}$	urea	$P_{ap}/_{urea}$
Experimental(n=5)	909±184	988±164	446±69	424±114
Meclofenamate(n=6)	1716±97*	1815±75*	820±22*+	827±56*
Time Control(n=6)	2133±140*	1678±90*	1203±128*	767±74*†

*p<0.05 vs Exp.;+p<0.05 vs Time Cont.;†0.1>p>0.05 vs U_{urea}

These results are consistent with the hypothesis that micropuncture-induced prostaglandins decrease papillary collecting duct permeability to water and/or urea or increase vasa recta blood flow. (Med. School Research Grant)

49.11

RENAL PROSTAGLANDIN (PG) SYNTHESIS IN THE BRATTLEBORO HOMOZYGOUS DIABETES INSIPIDUS (DI) RAT. Brian A. Jackson and Jeffrey W. Harrison*. Univ. of Kentucky, Lexington, KY 40536.

Previous studies in the DI rat have suggested that antidiuretic hormone (ADH) modulates renal PG synthesis. The specific sites of PG synthesis influenced by ADH have not been clearly defined. In the present study, prostaglandin E_2 (PGE_2) synthesis has been measured in inner and outer medullary slices, and collecting tubules microdissected from the inner medulla (PCD), outer medulla (MCT), and cortex (CCT) of DI rats and Long-Evans controls. For each rat, collecting tubules were microdissected from one collagenase digested kidney; inner and outer medullary slices were prepared from the contralateral kidney. Slices and tubules were incubated in 300 mOsm Krebs Ringers buffer at 37°C. PGE_2 synthesis (ng/30min/mg) was significantly lower in both inner medullary (1.09±0.2 vs 2.63±0.4; p<0.001; n=8) and outer medullary (0.07±0.01 vs 0.17±0.03; p<0.01; n=8) slices of DI rats compared to controls. PGE_2 synthesis (pg/20min/mm length) did not differ between DI rats and controls in either PCD (3.17±0.5 vs 2.55±0.5; n=6) or MCT (1.72±0.5 vs 2.21±0.3; n=7); PGE_2 synthesis was however significantly lower in CCT of DI rats compared to controls (2.62±0.4 vs 5.36±0.6; p<0.01; n=7). These data suggest that PGE_2 synthesis in medullary interstitial cells but not medullary collecting tubules may be modulated by ADH. PGE_2 synthesis in cortical collecting tubules may also be ADH sensitive. (Supported by AM 32395)

49.12

EFFECT OF ACUTE RENAL DENERVATION ON THE RENAL RESPONSES TO HEAD-UP TILT IN THE DOG. Thomas V. Peterson, Nancy L. Hurst*, Jamie A. Walla* and Patricia A. Frieden*. Dept. of Medical Physiology, Texas A&M University College of Medicine, College Station, TX 77843

Previous studies have shown that renal denervation abolishes the antinatriuretic response of the dog to short duration (10 min) head-up tilt thus demonstrating that these nerves elicit the initial decrease in sodium excretion which occurs with orthostasis. The present study was performed to determine the role of the renal nerves in mediating the renal responses to more prolonged tilt. Mongrel dogs were anesthetized with sodium pentobarbital and the left kidney acutely denervated. The right kidney served as the innervated control. Renal perfusion pressure was controlled by means of an aortic snare and maintained at or slightly above control levels during tilt. Each animal was subjected to 45° head-up tilt for 40 mins. with urine being collected every 5 mins. In the innervated kidney, significant decreases in urine flow, sodium excretion and fractional sodium excretion occurred throughout the tilt procedure and increased back to pre-tilt levels within 5 mins. after the dogs were returned to recumbency. In contrast, no decreases in renal excretion occurred in the denervated kidney during any tilt period. These results demonstrate that, in the dog, even when head-up tilt is performed for 40 mins., renal denervation abolishes the antidiuresis and antinatriuresis. (Supported by NIH Grant AM 27689 and the American Heart Association, Texas Affiliate).

EPITHELIAL TRANSPORT

50.1

EFFECT OF ETHANOL ON UPTAKE OF AMINO ACIDS INTO INTESTINAL BRUSH BORDER MEMBRANE VESICLES. Robert C. Beesley. University of Oklahoma Health Sciences Center, Oklahoma City, OK 73190.

Brush border membrane vesicles isolated from hamster jejunum by a Ca^{2+} precipitation technique were used to investigate the effects of ethanol on transport of amino acids across the brush border membrane. Imposition of an inwardly directed gradient of NaCl resulted in transient accumulation (overshoot) of L-alanine followed by a gradual decline to equilibrium levels. Ethanol reduced both the rate of uptake and the maximum accumulation without altering the final equilibrium level. Ethanol, 1%, 3% and 5%, reduced the overshoot by 14%, 25% and 30% respectively. Similar results were obtained when the effect of ethanol on uptake of L-phenylalanine was ascertained. The inhibitory effects of ethanol on amino acid uptake could be reversed by washing the membranes with ethanol-free media. When L-alanine uptake was measured in the absence of a NaCl gradient (NaCl equilibrated across the membrane) ethanol had no effect on the rate of uptake and the final equilibrium level attained. These results suggest that ethanol does not inhibit uptake of amino acids by direct interaction with the transport system but perhaps by increasing the permeability of the membrane thereby accelerating the rate of dissipation of the Na^+ electrochemical gradient.

50.2

TRANSCELLULAR NA TRANSPORT AND ELECTROLYTE HOMEOSTASIS IN FROG SKIN. R.L. Duncan*, C.O. Watlington, T.U.L. Biber and E.G. Huf. Medical College of Virginia, Richmond, VA 23298

This study was designed to determine to what extent active Na transport is coupled to electrolyte homeostasis in frog skin. The main objective was to separate these two cellular functions by applying fluoroacetate (FA), ouabain (OU) and vanadate (VA) over a wide range of concentrations and to observe correlation between electrical and flux measurements in whole skin and chemical measurements of cellular $[Na]_c$, $[K]_c$ and $[Cl]_c$ in split skins after a one hour incubation period. Control values for cellular electrolytes were: $[Na]_c$ 15-50 mM; $[K]_c$ 45-150 mM; $[Cl]_c$ 27-52 mM. $[Na]_c$ and $[K]_c$ were clearly complementary in that $[Na]_c + [K]_c$ remained remarkably constant at 129 mM. $[Cl]_c$ appeared to be nearly independent of $[Na]_c$. At high doses on both sides of the skin, OU and VA decreased skin PD, SCC (= net Na flux) and $[K]_c$, increased $[Na]_c$ and conductance while $[Cl]_c$ remained unaffected. High doses of FA, which acts from the blood side, decreased all electric parameters of the skin, but had no effect on cellular electrolytes. OU, at 10^{-6}M, significantly decreased transport but had, at best, only a marginally significant effect on cellular electrolytes. All concentrations of VA which affected transport also affected cellular electrolytes. These results indicate that transcellular active Na transport and cellular electrolyte homeostasis are not always rigidly coupled. This may be because these processes are not uniformly distributed within the cells or among the cell layers.

50.3

EFFLUX OF Cl-36 FROM CHOROID PLEXUS BY CHLORIDE-BICARBONATE EXCHANGE. C.E. Johanson* and Q.R. Smith* (SPON: S.J. Fidone).
Dept. of Pharmacology, Univer. of Utah School of Medicine, Salt Lake City, UT 84132.

The efflux of Cl-36 was analyzed in adult rat lateral ventricle choroid plexus (LVCP) incubated in synthetic CSF at 37° C. After steady-state loading of Cl-36, radioisotope washout from in vitro LVCP was quantified by efflux rate constant (k_o, sec^{-1}) analysis. Control values of 0.057 and 0.226 sec^{-1} were determined for Cl-36 and H-3 sucrose (marker for extracellular washout). The disulfonic stilbenes (SITS and DIDS, 1 mM), as well as furosemide (1 mM) and acetazolamide (0.1 mM), inhibited Cl-36 k_o by 35-55%. Acetazolamide (0.1 mM) inhibited Cl-36 efflux into CSF containing either Cl-HCO_3 or isethionate-HEPES as the major anions. At 15° C, Cl-36 efflux rate was only 49% that at 37° C. CSF medium anion replacement (isethionate and HEPES for Cl and HCO_3, respectively) reduced Cl-36 k_o by 57%. In the pH study, there was a progressively greater inhibition of Cl-36 efflux as CSF pH was varied from 8.2 (k_o 0.07 sec^{-1}) to 6.7 (0.026 sec^{-1}). The results strongly indicate that Cl-36 is extruded from LVCP by a Cl-HCO_3 exchanger. (Supported in part by NIH NS 13988.)

50.4

INTERCELLULAR SPACE (ICS) PRESSURE MODULATES ALTERATION IN TIGHT JUNCTION (TJ) PERMEABILITY INDUCED BY CYCLIC AMP IN NECTURUS GALLBLADDER (GB). C.E. Palant,* and C.J. Bentzel, VA Medical Center and SUNY/Buffalo, Buffalo, NY 14215.

Mucosal 8-bromo-cyclic AMP (8Br-cAMP) induces reversible changes in TJ permeability and structure in Necturus GB. Electrophysiological responses to 8Br-cAMP were studied when ICS were collapsed or dilated. When GB were bathed in NaCl Ringers and serosal outflow pressure decreased by 3 cm H_2O, tissues fixed in glutaraldehyde revealed ICS collapse and increased TJ depth (freeze fracture EM) as compared to GB fixed with outflow pressure at +1 cm H_2O. Increased TJ depth was due to extension of intramembranous strands into the basolateral membrane below the meshwork. Electrophysiological response to 8Br-cAMP (10^{-3} M) was enhanced when ICS were collapsed. This was not exclusively due to decreased ICS width since raising outflow pressure did not alter steady state transepithelial resistance (R_t) or PD (ψ_{ms}). BUMETANIDE (BUM) (10^{-4} M) (which decreases NaCl coupled H_2O flow) reversibly decreased control ψ_{ms} and short circuit control (I_{sc}) but not R_t. BUM increased R_t in 8Br-cAMP treated tissues by 25% at all concentrations tested. BUM did not ablate increments in ψ_{ms} and I_{sc} induced by 8Br-cAMP.

Conclusions: 1) Decreased ICS pressure results in vertical expansion of TJ meshwork and augments response to cyclic AMP. 2) Although BUM enhances paracellular effects of 8Br-cAMP, it does not alter transcellular response. (supported by C. Culpeper Foundation, VA Research and #1-R01-AM31552-01A1).

50.5

SEROSAL Cl^- MODULATES BASOLATERAL MEMBRANE K^+ CONDUCTANCE IN NECTURUS GALLBLADDER. **V. Lyall* and W. McD. Armstrong.** Dept. Physiol. and Biophys., Indiana Univ. Sch. Med., Indianapolis, IN 46223.

There is evidence that luminal Cl^- replacement by less permeant anions enhances apical membrane K^+ conductance in Necturus gallbladder. To study possible Cl^- effects on basolateral K^+ conductance, gallbladders were mounted at 23° C between identical oxygenated solutions containing, in mM, 100 NaCl, 5.4 KCl, 1.8 $CaCl_2$, 16 mannitol, buffered to pH 8.2 with imidazole. Apical membrane potential (V_a) was measured with microelectrodes and corrected, where necessary, for changes in liquid junction potentials. Replacement of 80 mM serosal NaCl with KCl (total K^+ 85.4 mM) reversibly depolarized V_a (59±1 mV, S.E.) by 26±1 mV. Following complete replacement of serosal Cl^- by gluconate, V_a was 55±2 mV. Increased serosal K^+ (85.4 mM) depolarized V_a by 16+1 mV. This attenuated response was unchanged (17±1 mV) when both mucosal and serosal Cl^- were replaced by gluconate but was not seen when mucosal Cl^- alone was replaced (25±1). Similar, though smaller, effects were observed at pH 7.2. Since the basolateral membrane of Necturus gallbladder is known to behave as an almost ideally K^+-selective membrane, these effects are consistent with a decrease in basolateral K^+ conductance following removal of serosal Cl^-. Similar effects were found in Necturus intestine at pH 7.2. Supported by USPHS AM 12715.

SHOCK

51.1

DOSE RESPONSE EFFECTS OF PROSTAGLANDIN D_2 IN THE DOG. P.S. Rao, J. Dietz, K. Marsden*, D. Cavanagh* and E. Spaziani*. University of South Florida College of Medicine, Tampa, Fl 33612

Prostaglandin D_2 (PGD_2) was originally thought to be an inert product of endoperoxide inactivation, but there is now ample evidence to show that exogenous PGD_2 has significant biological activity. This study was designed to evaluate the dose response effects of intravenous PGD_2 on various parameters in the anesthetized dog. Group 1 received PGD_2 dissolved in phosphate buffered saline (PBS,pH8.0) at increasing dose levels (0.125,0.25,0.5 and 0.75 μg/kg/min) for a period of 30 minutes each, with a 30-minute period allowed for recovery between infusions. Group 2 received only PBS similar to that of Group 1 and served as controls. The study parameters included mean aortic pressure (MAP), pulmonary artery pressure (PAP), heart rate, renal artery flow (RAF), creatinine clearance (Ccr), plasma sodium and potassium, urinary sodium and potassium,urinary output, plasma renin activity (PRA), arterial PO_2, PCO_2 and pH. In the control group all parameters remained stable during the study period except a progressive increase in the MAP. In the group receiving PGD_2, a dose-dependent increase was observed in the RAF, Ccr, PRA, urinary output and sodium and potassium excretion. Pa O_2 decreased as the rate of PGD_2 infusion increased. These results show that 0.5 μg/kg/min of intravenous infusion of PGD_2 is sufficient to improve renal perfusion without undue adverse effects on the pulmonary vascular bed or significant changes in MAP. Thus, judicious intravenous administration of PGD_2 may have some clinical application in circulatory shock when renal function is compromised.

51.2

THROMBOXANE DOES NOT PLAY A ROLE IN LETHALITY OF E. COLI SEPSIS. D.C. Morgan*, W.C. Wise, P.V. Halushka*, J.A. Cook. Departments of Physiol., Pharmacol., and Medicine, Medical University of South Carolina, Charleston, SC 29425

Elevated thromboxane (TxA_2) and prostacyclin (PGI_2) synthesis has been observed in rats with rapidly lethal endotoxemia or fecal peritonitis. A new model was developed to facilitate the quantitation of bacteremia and the study of eicosanoid levels over a longer period of time. Gauze contaminated with 10^9 E. coli in saline was implanted in the abdomen of 200g female rats. Gauze with sterile saline was implanted in sham animals. Plasma TxA_2 and PGI_2 were measured by RIA of their stable metabolites, TxB_2 and 6-keto-PGF_{1a} (6-keto), respectively.

		Control	Septic	Sham
TxB_2 (pg/ml)	1hr	262±91(4)*	1197±336(8)	1083±232(9)
	8hr		772±139(7)	652±109(9)
6-keto (pg/ml)	1hr	115±41(3)	561±110(7)*	57±16 (3)
	8hr		2234±259(7)*	143±88 (4)
Mortality	24hr	0%	68%*(16)	0%(8)

*p<0.05 vs. sham Mean±SEM ( )=n

TxB_2 levels were the same in sham or septic rats despite a significant difference in mortality. Elevated 6-keto was associated with high mortality in sepsis, but was absent in sham animals. Conclusions: TxA_2 is probably not an important mediator of death in rat sepsis. Further studies are needed to clarify the role of PGI_2 in septic shock. (Supported: NIH GM27673 & HL29566).

51.3

EFFECTS OF PH-4.25 IgG TREATMENT ON BLOOD PRESSURE (ABP), HEART RATE (HR) & BLOOD ACID-BASE VARIABLES DURING BACTEREMIC SHOCK IN RATS. J.M.Lurton*,M.S.Collins*,R.M.Raymond & T.E. Emerson,Jr. Cutter Group of Miles Labs,Inc.,Berkeley,CA.94710 and Loyola Univ. Med. Ctr., Maywood, IL. 60153.

We have shown previously that pretreatment (i.p.) with a recently developed native 5% IgG preparation for i.v. use (IGIV-pH4.25) prevents hypotension, acidosis & death during Salmonella typhimurium bacteremia in rats. The present study characterizes effects of IGIV-pH4.25 treatment on variables in hypotensive, metabolically compromised rats. S-D rats (250-300g) were injected i.p. with 1.2x10 bacteria; measurements were made under Nembutal anesthesia 2-5 days after infection. IGIV-pH4.25 was infused i.v. at 0.02ml/min for 2 hrs. (500 mg/kg IgG; N=5). Control bacteremic (N=5) and non-bactermic (N=5) rats received equivolume i.v. infusions of albumin (500 mg/kg). Preinfusion data are depicted below; all variables are in standard units & BE= base excess.

	ABP	HR	pH	PCO2	HCO3-	BE
ALBUMIN (Normal)	112	350	7.45	43	29	+5.1
ALBUMIN (Bacteremic)	62	410	7.46	31	22	-1.2
IGIV (Bacteremic)	64	428	7.42	31	20	-3.7

No variable changed significantly during the 2hr albumin or IgG infusion. These data show that rats in bacteremic shock tolerate a high i.v. infusion of low ph IgG with no further deterioration of ABP or any measured acid-base variable. This study and earlier work suggest that IGIV-pH4.25 has excellent potential for treatment of gram-negative sepsis.

51.4

EFFECTS OF ENDOTOXIN ON THE LEFT VENTRICULAR END-SYSTOLIC PRESSURE-WALL THICKNESS RELATIONSHIP IN ANESTHETIZED DOGS. P.M. Kober, D.V. DeFily*, H.K. Jacobs, R.M. Raymond and J.X. Thomas, Jr. Loyola Univ. Med. Center, Maywood, IL 60153

Myocardial performance during endotoxin shock was analyzed by the LV end-systolic pressure-wall thickness relationship (ESPT) in open-chest, pentobarbital anesthetized dogs. A lead II EKG, systemic arterial pressure, LV pressure (P-7 Konigsberg), LV dP/dt, and LV anterior wall thickness (sonomicrometer) were measured. End systole was defined as the pressure and wall thickness coincident with peak -LV dP/dt. To describe the ESPT relationship, preload and afterload were varied with occluders while the respirator was momentarily stopped at end-expiration. After control measurements, dogs were given 1 mg/kg endotoxin (S. enteritidis). Measurements were taken every 15 min. until death. Data was grouped into early, middle, late, and terminal phases of shock as a % of the time to death. The ESPT slope was either unchanged or increased (i.e. a greater negative slope) from control through the late phase of shock (reaching 242±114% of control by the late phase, control slope -20±2 mmHg/mm). This slope was depressed below control only during the terminal phase (-10±1 mmHg/mm). Myocardial contractility is not depressed except as a terminal event and the early depression of circulatory performance is likely due to decreased venous return and/or metabolic defects, which ultimately leads to death. (Supported by E.M. Bane Trust Fund and Hines V.A. Hospital).

51.5

ACUTE CARDIAC ARREST DURING ENDOTOXIN SHOCK IN UNANESTHETIZED DOGS. D.M. Klein, D.A. Gibbons*, P.M. Kober, M.W. Gerdish*, H.K. Jacobs and R.M. Raymond. Depts of Surgery and Physiology Loyola Univ. Med. Ctr., Maywood, Il. 60153 and The VA Hospital Hines, Il. 60141.

Altered myocardial substrate utilization and global ischemia have been reported to occur in anesthetized dogs during endotoxin shock. The objective of this study was to determine myocardial hemodynamic changes, oxygen utilization, and acid-base status during the progression of shock in unanesthetized dogs. One day following surgery control determinations were made. Shock was induced by the I.V. injection of 1 mg/kg S. enteritidis endotoxin. Animals were monitored until death. Results are listed in the following table (*=p < 0.5 vs. control; A-V=arterial-coronary sinus difference).

Table

Time (hours)	Control	1	2	3	4
Cardiac Index (L/min/M^2)	3.0	2.5*	1.9*	2.0*	1.9*
Mean Arterial Pressure (mmHg)	87	53*	48*	53*	60*
Circumflex Flow (ml/min/100g)	50	35.8*	45*	39	40
Cardiac O_2 Uptake (ml/min/100g)	4.8	3.4	5.2	4.4	5.0
A-V pO_2 (mmHg)	68	63	57	68	74
A-V LDH (IU/L)	-126	-113	-51	165	-147
A-V SGOT (IU/L)	-88	-123	14	-113	-3

Dogs died in acute cardiac arrest. Myocardial autopsy revealed either diffuse or localized areas of hemorrhage. From these data it is concluded that there is no evidence of global myocardial ischemia.

51.6

IMPROVED LEFT VENTRICULAR CONTRACTILITY WITH NALOXONE TREATMENT IS INDEPENDENT OF CARDIAC LOAD IN CANINE HEMORRHAGIC SHOCK. N.J. Gurll, A. Kamhawy*, A. Stoltz*, and D.G. Reynolds. Univ. Iowa Coll. Med. and VAMC, Iowa City, IA 52240

Naloxone (nal) improves mean arterial pressure (MAP, mmHg), cardiac output (CO, L/min), and the maximum rate of change of left ventricular pressure (LV dp/dt max, mmHg·10^3/sec) in canine hemorrhagic and endotoxic shock. The latter response may be a function of preload, afterload, or myocardial contractility. Dogs were anesthetized with pentobarbital and bled into a reservoir to a MAP of 45 mmHg (t=0). MAP was maintained (constant afterload) by the reservoir until t=120 min when shed blood was reinfused. Animals were treated with either 0.9% NaCl (N=5) or nal 2 mg/kg bolus plus 2 mg/kg·hr infusion iv (N=8) from t=60 to 270 min. Nal increased LV dp/dt max despite constant afterload and preload (unchanged CO and cardiac filling pressures):

		baseline	t=0	60	75	90 min
LV	NaCl	3.61±.72	1.12±.18	1.99±.44	2.35±.65	2.35±.50
dp/dt	nal	2.95±.24	1.10±.08	1.71±.14	3.28±.38	3.01±.41
CO	NaCl	3.45±.63	0.69±.09	0.71±.09	0.79±.09	0.72±.09
	nal	2.52±.10	0.75±.09	0.66±.12	0.69±.11	0.64±.12

The increase in LV dp/dt max after treatment at t=60 was significant for nal but not for NaCl. Therefore nal increases LV dp/dt max by increasing cardiac contractility independent of preload and afterload. These data suggest the naloxone effect is on the heart.

51.7

NON-ISCHEMIC MYOCARDIAL DAMAGE IN ENDOTOXIN SHOCK. M.W. Gerdish*, D.A.Gibbons*, D.M.Klein, H.K. Jacobs, R.M.Raymond, and J.X. Thomas, Jr. Depts. Physiology and Surgery, Loyola University Med. Ctr. Maywood, Il. 60153

Global myocardial ischemia has been proposed as a major contributing factor to myocardial failure in endotoxin shock. The present study was designed to further test this hypothesis. Shock was induced with an LD100 (1 mg/kg) dose of endotoxin (S. enteriditis) in open chest pentobarbital anesthetized dogs. Six dogs were instrumented to measure hemodynamic and metabolic parameters. There were progressive and significant decreases in cardiac index (71%), arterial pressure (64%), and coronary flow (38%); p<0.05). Systemic LDH, SGOT and alkaline phosphatase increased throughout the protocol, but arterial-venous difference did not increase across the heart. Apparently, no cardiac cellular disruption occurred during the protocol. Reduction in metabolic efficiency was evident since MV02 was unchanged even with reduced external work. Although the lack of pH, SGOT and LDH changes are consistent with adequate levels of blood flow, prominent surface and intramyocardial hemorrhages were observed. Thus, gross myocardial injury may occur in endotoxin shock, progressive global ischemia does not appear to be the cause. (Supp: E.M. Bane Charitable Trust and V.A. Funds).

51.8

MYOCARDIAL HEMODYNAMICS AND CARBOHYDRATE METABOLISM PRECEDING CARDIAC ARREST DURING ENDOTOXIN SHOCK IN UNANESTHETIZED DOGS. R.M. Raymond, D.A. Gibbons*, T.E. Emerson, H.K.Jacobs and D.M. Klein. Loyola Univ. Med. Ctr., Depts. of Surgery & Physiology, & Hines, V.A. Hosp.,Hines, Il 60141 & Miles Labs., Berkeley, CA 94710

Previously, others have reported myocardial derangements in anesthetized dogs during endotoxin shock. The present study was undertaken to determine myocardial hemodynamics and metabolism during endotoxin shock in unanesthetized dogs. Mongrel dogs (N=10) were implanted with aortic and circumflex flow (Q) probes and catheters were placed for sampling of arterial (A) and venous glucose (G), lactate (L), and O_2 uptake (U) by the heart. One day following surgery, control measurements were taken. Shock was induced by the IV injection. Myocardial autopsy revealed areas of localized or diffuse hemorrhage. (*p < 0.05 vs. control).

Time (hours)	Control	1	2	3	4
Mean A Pressure (mmHg)	87	53*	48*	53*	60*
Body Temperature (°C)	39.4	40.3*	40.9*	40.9*	40.2*
Circumflex Flow (ml/min/100q)	50	35	45	39	40
Cardiac V O_2 (ml/min/100g)	4.8	3.4	5.2	4.4	5.0
Cardiac G U (ml/min/100g)	0.5	0.5*	1.0*	0.1	0.7
Cardiac L U (mg/min/100g)	3	54*	64*	45*	59*

From these data it is concluded that cardiac arrest from endotoxin shock is not the result of ischemia but rather the result of an acute metabolic deficit.

51.9

PREVENTION OR AMELIORATION OF CARDIOVASCULAR & METABOLIC ABNORMALITIES BY FIBRONECTIN (FN) TREATMENT DURING ENDOTOXIN SHOCK IN THE DOG. T.E.Emerson,Jr., M.M.Everett*, J.G. Hauptman* and R.M.Raymond. Cutter Group of Miles Labs, Inc. Berkeley, CA. 94710, Mich. State Univ. Vet.Coll.,E.Lansing, MI. 48824 & Loyola Univ. Med. Ctr., Maywood, IL. 60153.

Previous work by us suggests that pre-treatment with FN is protective in rats during endotoxin (endo) shock (Fed. Proc. 43:1025,1984). The present study was to explore possible mechanisms by which FN treatment is efficacious during endo shock. Dogs were anesthetized (Nembutal) and arterial blood pressure (ABP), cardiac output (CO), heart rate, total peripheral resistance, stroke volume & work, and blood glucose, pH, HCO3-, PO2, PCO2 & base excess were determined for 6 hrs post-endo. Purified human FN (50 mg/kg) was given i.v. prior to i.v.injection of E. coli endo (0.5 mg/kg; N=8). Control animals received saline instead of FN (N=4). Changes in both groups were similar during the first 30-60 min post endo; however, beyond this time cardiovascular and other variables were either near normal or markedly less abnormal in the FN group. A striking difference between the groups was that in most FN treated dogs, ABP, CO & blood glucose were near pre-endo values or within the "normal" range at 6 hrs post-endo. These data support earlier observations that FN pre-treatment affords protection during endo shock and suggest that mechanisms of protection are either directly or indirectly related to improvement in both cardiovascular and metabolic function.

51.10

HYPERTONIC SALINE PROLONGS SURVIVAL IN A CLINICALLY RELEVANT HEMORRHAGE MODEL. S.J.HOLLENBACH* AND L.W.TRAVERSO. LETTERMAN ARMY INSTITUTE OF RESEARCH, SAN FRANCISCO, CA 94129

Hypertonic saline (7.5% NaCl, HS) has reversed fatal canine hemorrhagic shock (Wigger's model). We have developed a fixed volume, 100% fatal, unanesthetized, swine hemorrhage (HEM) model which mimics the survival rate of trauma victims. Blood (54ml/kg) was removed in 15±2 min. We tested the effect of HS versus normal saline(0.9% NaCl, NS) on survival rate, pO2, pCO2, pH, bicarbonate, lactate(LACT), hematocrit (Hct), blood pressure (BP), and heart rate. Immediately after HEM, a % of the shed blood (SBR) was replaced into a central vein: 14% SBR as HS(n=10) or as NS(n=15) each in 5 min, 25% SBR as HS(n=10) or 25% SBR as NS(n=10) each in 10 min. The survival rate of HS was > NS - 14% SBR:p=0.134, 25% SBR:p=0.007 (Mantel-Cox statistic). Survivors to 24 hours were present only in the HS groups (14% SBR - 3/10, 25% SBR - 2/10). Different values (p<0.05) were seen at 15 min after HEM for the 25% SBR groups:

	pCO2(TORR)	Hct(%)	BP(TORR)	LACT(mg/dl)
HS	28±8	13±2	57±9	112±32
NS	14±5	19±4	38±11	180±30

Also, LACT differences (p<0.05) were found at 30 min after HEM in the 25% SBR groups: HS=95±46, NS=188±33 mg/dl; and at 15 min in the 14% SBR groups: HS=144±42, NS=188±20 mg/dl. Compared to NS controls, HS is associated with a lower Hct and LACT, and by a higher BP, pCO2, and survival rate. Therefore, HS appears to prolong survival after fatal HEM by increasing transcapillary refill and intravascular volume.

51.11

TRANSCAPILLARY REFILL DURING HEMORRHAGIC HYPOTENSION IN THE CONSCIOUS PIG. Carol A. Bossone* and John P. Hannon. Letterman Army Institute of Research, Presidio of San Francisco, Ca. 94129.

Under near-basal conditions 38.5±0.09 (mean ± SEM) ml/kg of blood was progressively removed over a one hour period from 8 conscious pigs (22.4±0.39 kg); 7 to 10 days previously chronic carotid artery catheters were implanted and the pigs were splenectomized. During hemorrhage mean arterial pressure decreased from 98±2.9 to 48±1.5 mmHg and over a subsequent 4 hour recovery period it rose to 72.0±2.9 mmHg. Over the same time intervals plasma volume decreased from 50.7±1.21 to 35.4±1.30 and rose again to 40.4±1.93 ml/kg. Transcapillary refill became evident while blood was being lost and by the end of hemorrhage amounted to 13.0±0.67 ml/kg. After a 4 hour recovery it was 18.1±1.11 ml/kg. Thus, transcapillary refill replenished 45.8% of the plasma lost over the one hour hemorrhage period and an additional 17.9% over the 4 hour recovery period. Total plasma protein decreased from 2.86±0.07 to 1.65±0.07 g/kg during hemorrhage, but rose to 1.95 g/kg during recovery. Total protein exceeded predicted values by 31% at the end of hemorrhage and by 54.8% at the end of the recovery period. Hemorrhage led to an 11.3±0.94 mOsm/L increase in plasma osmolarity, attributable in part to hyperglycemia (4.2±0.58 mM/L increase) and in part to hyperlactacidemia (8.2±0.87 mM/L increase). It was concluded that transcapillary refill was attributable to Starling effects enhanced in part by interstitial hyperglycemia and in part by a transfer of protein from the interstitial space to plasma.

51.12

RADIATION-INDUCED CHANGES IN REGIONAL BLOOD FLOW IN RHESUS. F.A. Meeks*, W.A. Alter, III, R.N. Hawkins, R.R. Eng, J.T. O'Neill and C.N. Catravas. USUHS and AFRRI, Bethesda, MD

Exposure to supralethal doses of ionizing radiation has been shown to cause profound cardiovascular (CV) dysfunction in man and monkeys. This study was undertaken to evaluate changes in blood flow distribution during radiation-induced hypotension. Chloralose-anesthetized rhesus (n=7) were prepared for microsphere (15 µm) injections and to record CV parameters. Baseline physiological data included mean arterial pressure (MAP)=116±4 mmHg (±SEM), cardiac index (CI)=156±13 ml/min/kg, and the following blood flows (ml/min/100g tissue): epicardium (EP), endocardium (EN), cerebrum (CE), hypothalamus (H), medulla (M), ileum (I), spleen (S), kidney cortex (K), adrenal (A), and pancreas (P). Within 5 min after whole-body exposure to 4000 rads (R) of gamma radiation, MAP and CI decreased by 58±2 and 51±5%, respectively. At this time percent decreases in regional blood flows were: EP=39±8, EN=51±7, CE=43±16, H=64±14, M=61±18, I=26±11, S=93±3, K=45±9, A=27±13, and P=60±10. By 90 min post R, MAP and CI recovered to 73±7 and 59±6% of their respective baselines. Perfusion of heart, brain, and most other organs remained depressed but I and A flows were increased above baseline. In contrast sham-R rhesus (n=4) did not experience significant decreases in any of these parameters. These findings support the hypothesis that hemodynamic changes after exposure to 4000 rads are generally similar to those seen in other forms of shock.

COMPARATIVE PHYSIOLOGY: OSMOTIC AND IONIC REGULATION

52.1

ENVIRONMENTAL MODULATION OF AN EPITHELIAL PARACELLULAR PATHWAY. David J. Prior. Univ. of Kentucky, Lexington, KY. 40506.

Due to their moist integument, terrestrial gastropods can experience rapid dehydration. During progressive dehydration the osmolality of their hemolymph increases exponentially. They can recover by absorbing water through the surface of the foot while in contact with a moist substrate. The rate of uptake of ^{14}C-inulin during this process of contact-rehydration parallels that of water absorption, indicating the involvement of a paracellular pathway. Water absorption during this "drinking behavior" occurs at the normal rate of about 20-50 ul/cm min only if the osmolality of the substrate is below 100 mOsm/Kg H_2O(with mannitol). This is not simply a function of the difference in osmotic gradients because when the osmolality of the substrate was 600 mOsm/Kg H_2O there was little net efflux of water. Thus it seems that the efficacy of this epithelial paracellular pathway can be modulated by the osmotic properties of both the internal and external environments. (Supported by the Whitehall Foundation and an N.I.H.-R.C.D.A.).

52.2

PRELIMINARY ISOLATION OF A NATRIURETIC FACTOR FROM MOSQUITO HEADS. D.H.Petzel*,H.H.Hagedorn*, and K.W.Beyenbach. Cornell Univ., Ithaca,NY,14853

Dibutyryl-cAMP stimulates diuresis in isolated Malpighian tubules of Aedes aegypti by increasing the rate of fluid secretion in parallel with an increased rate of Na secretion and the hyperpolarization of the transepithelial voltage (V_t) to more lumen positive values(J.Comp. Physiol.,in press,1984). We now report the HPLC isolation of a factor from the head of mosquitos which mimics the action of cAMP. Control V_t averaged 52±2 mV(n=72), lumen positive. The HPLC factor eluting at 31% acetonitrile(CH_3CN) in a gradient of 0-60% CH_3CN caused a brief (10 sec) depolarization to 34±8 mV(n=7 columns, 7 tubules) followed by a sustained hyperpolarization of V_t to 66±5 mV(n=7 columns,7 tubules). In the Ramsay assay this factor significantly increased NaCl and fluid secretion without affecting K secretion.

SECRETION OF	CONTROL	HPLC FACTOR	
fluid,nl/min	0.65±.03(44)	2.3±0.2(12)*	mean±S.E.
Na, pmol/min	51±4(44)	344±35(12)*	(n=tubules)
Cl, pmol/min	119±6(44)	416±33(12)*	*p < 0.001
K, pmol/min	75±4(44)	68±10(12)	

Since the factor selectively stimulates active Na secretion we would like to name this factor the mosquito natriuretic factor (MNF) which presumably stimulates natriuresis via an increase in intracellular cAMP. Supported in part by NIH AI 14771 to HHH, NIH AM26633 and NIH AM 31291 to KWB and a National Kidney Foundation Fellowship to DHP.

52.3

FUNCTIONS OF THE LOWER GUT IN THE TERRESTRIAL SLUG, ARIOLIMAX COLUMBIANUS. I.Deyrup-Olsen and A.W.Martin.Univ. of Washington, Seattle, Wa. 98195.

Digestive systems of pulmonate molluscs have been studied fairly extensively from the buccal apparatus to the stomach. Relatively less is known of the function of the lower tract: intestine and rectum. We have investigated these structures in the large land slug Ariolimax columbianus (body weight up to 62 g). Analysis of these viscera showed that glucose and amino acids were present in variable amounts in intestinal fluid; its osmotic pressure (202± 39 mOsmol/l,n=12) did not differ significantly from that of blood (188 ± 27 mOsmol/l, n=28). These results indicated that the intestine is an important site of absorption of organic nutrients. The rectum was normally filled with dilute fluid (50± 20 mOsmol/l, n= 21) containing neither glucose nor amino acids. It may serve as a water reservoir for slugs exposed to water stress. We have tested the movement of fluid, with lumen-to-serosa osmotic gradient = 1/4 (serosal fluid = normal slug Ringer's solution), from sacs of intestine and rectum in vitro. Although the transfer of fluid was approximately the same from intestinal and rectal sacs under control conditions, this movement was enhanced significantly in the rectum, but not in the intestine, by acute dehydration, or rapid blood loss, as well as by serosal application of norepinephrine, 5-hydroxy tryptamine, and arginine vasotocin (1 nmol to 1 umol/ml).

COMPARATIVE PHYSIOLOGY: TEMPERATURE ADAPTATIONS

53.1

CHANGE IN ONCOTIC PRESSURE DUE TO TEMPERATURE. P. Glenn Tremml* and Arthur B. DuBois. John B. Pierce Foundation Laboratory, New Haven, CT. 06519

Fluid is held in the vasculature with the aid of an osmotic pressure created either directly or indirectly (Donnan effect) by plasma proteins. This is oncotic pressure. Oncotic pressure or colloid osmotic pressure (COP) of plasma is often measured using a membrane manometer (oncometer). If values obtained at room temperature have to be corrected to physiological temperatures, van't Hoff's Law (π = nRT/V) is generally assumed to be valid for making the correction. It predicts a 0.3%/°C change in osmotic pressure at 25°. The literature, however, is devoid of any data to substantiate the use of this factor. Experimentally, plasma oncotic pressure measurements were made on human serum albumin (5g/dl saline) and on separated plasma from 0 to 50°C, using a Weil Oncometer System 186 modified with a water jacket connected to a variable temperature water bath. Over the range 10-40°C the colloid osmotic pressure of albumin changed 0.11%/°C and the plasma 0.22%/°C. The mean for albumin was 18.0 mmHg and for plasma was 28.0 mm Hg at 25°C. The change of pressure with temperature was less than predicted from van't Hoff's law. The dependence of oncotic pressure on protein charge, which varies with temperature due to pH, protein tertiary structure, and chloride binding, theoretically contribute to deviations from van't Hoff's law.

53.2

PHOSPHOLIPASE A_2 FROM THERMALLY ACCLIMATED TROUT: EVIDENCE FOR A DEACYLATION-REACYLATION CYCLE IN MEMBRANE RESTRUCTURING. Nancy P. Neas. Colgate University, Hamilton, New York 13346.

Phospholipase A_2 (PLA_2) was extracted from liver microsomes of both 5° (CA) and 20°-acclimated (WA) trout (Salmo gairdneri) using Triton X-100, followed by precipitation with 35-65° ammonium sulfate and Sephadex G-200 chromatography in the presence of 0.5% Triton X-100. This resulted in a 30-fold purification and the removal of all traces of phospholipid from the enzyme of both WA and CA trout. Column elution profiles were similar for both acclimation groups, yielding a molecular weight estimate for the enzyme of 73,000. Kinetic measurements of PLA_2 from WA and CA indicated compensation for temperature below V_{max} in both the particulate (microsomal) enzyme and the lipid-free protein. This was due to decreased apparent K_m values in CA fish, regardless of the temperature of the assays. These adaptations could not be attributed to the interaction of the enzyme with the membrane lipids, but to qualitative changes in the enzyme that resulted from acclimation. Other adaptive qualities of PLA_2, such as reduced K_m in response to acute decreases in temperature in WA fish, were only apparent in particulate preparations, and thus were a function of the protein-lipid complex. These data suggest that an acclimation-induced increase in the activity of PLA_2 may result in the activation of a deacylation-reacylation cycle at cold temperatures.

53.3

THE ROLE OF DESATURASE ENZYMES IN THERMAL ACCLIMATION OF RAINBOW TROUT. Arthur F. Hagar* and Jeffrey R. Hazel . Arizona State University, Tempe, AZ 85287

The role of desaturase enzymes in the thermally-induced restructuring of microsomal membranes was investigated in liver tissue of rainbow trout. Fish were acclimated to 5° or 20°C, and then transferred to the opposing temperature. For one month following the transfers the microsomal fatty acid composition and the activities of the Δ9, Δ6, and Δ5 desaturase enzymes were monitored. Enzyme activities were measured by incubation of labelled substrate with microsomal preparations; substrate and product were then separated by radiogaschromatography.

Transfer of trout between acclimation temperatures did not result initially in significant alterations in desaturase activity. Changes in the relative proportions of saturates (both directions) and polyunsaturates (5° to 20°C), however, did occur during the first three days after transfer, indicating that a deacylation-reacylation mechanism is responsible for the short-term adaptation of microsomal fatty acid composition to temperature changes. Alterations in Δ9 (both directions) and Δ5 (5° to 20°C) desaturase activities were correlated with fatty acid compositional changes 2-4 weeks after the change in temperature, suggesting that these enzymes may play a role in the latter stages of thermal acclimation. This work was supported by NSF Grant # PCM-8301757.

54.1

A VARIABLE LINEAR AIRFLOW RESISTOR FOR RESPIRATORY LOADING STUDIES. E.M. Sivieri*,V.K. Bhutani, S. Abbasi*, T.H. Shaffer. Sect. Newborn Pediatrics, Pennsylvania Hospital., Univ. PA Sch Med., Philadelphia, PA 19107.

The effects of known added loads on the ventilatory parameters have been previously studied in adults and newborns. To simplify the administration of a purely resistive load, a newly designed variable linear resistor was utilized and evaluated in preterm neonates. The resistor is constructed from two concentric lab pipettes (outer pipette: 0.7 cm I.D., inner pipette: 0.6 cm O.D.). The inner pipette is occluded and lined with three equally spaced thin plastic strips running longitudinally along its surface to maintain concentricity with the outer pipette. By varying the overlap between the pipettes the resistance changes proportionally. Test results indicate that resistances of 50 to 300 cm H_2O/L/sec could be obtained over an airflow range of 0.5 to 4 L/min with a nonlinearity of < 0.8%. Inspiratory resistive loads of 100 (R_1) and 300 (R_2) cm H_2O/L/sec were applied for 2 min to 9 growing preterm neonates ($\bar{x}$± SEM values) 49 ± 7 days old, 1.8 ± 0.1 kg study weight. Pulmonary mechanics and ventilatory parameters were determined prior to and during the loading. A significant increase ($p < .05$) in the work of breathing ($\bar{x}$ ± SEM) was observed from 2.87 ± 0.56 to 4.52 ± 0.78 kg-cm/min/kg with R_1 (57.7%); and from 2.86 ± 0.36 to 5.41 ± 0.91 kg-cm/min/kg with R_2 (88.8%). These observations demonstrate that the device is simple to construct, easy to use, and provides a constant resistive load insensitive to changes in airflow.

54.2

COMPARATIVE EFFECTS OF PROSTAGLANDINS D_2 AND D_3 ON FETAL PULMONARY AND SYSTEMIC CIRCULATIONS. Gerald E. Gause*, Mary Tod*, and Sidney Cassin. Department of Physiology, College of Medicine, University of Florida, Gainesville, FL 32610.

Resistance to blood flow was measured in unventilated lungs of fetal lambs. Fetuses were delivered by cesarean section from chloralose-anesthetized ewes with the umbilical circulation maintained intact. The lower left lobe was isolated in situ and pump perfused at constant flow. All procedures were carried out under deep surgical plain of anesthesia. Infusions of PGD_2 or PGD_3 directly into the left pulmonary artery (LPA) at 0.14 ug/kg min for 1 min reduced pulmonary vascular resistance (PVR) by 11% and 30% respectively. At the higher dose of 6.6 ug/kg min these drugs produced decreases in PVR of 41% and 59%, respectively. Infusions of PGD_2 or PGD_3 at the same doses into the jugular vein produced similar but attenuated responses in a dose dependent manner. Thus, the response to PGD_3 infused for 1 min into the LPA at the highest dose tested is equivalent to the decrease in PVR occurring with the initiation of respiratory. Mean systemic arterial pressure usually decreased slightly (<5%) for all infusion rates of PGD_3 and usually increased slightly (<5%) for both LPA and jugular infusions of PGD_2. These data suggest that these compounds may be of value in reducing pulmonary hypertension in the immediate neonatal period and should be evaluated further for possible clinical application. Supported in part by NIH HL 10834.

54.3

STRESS RELAXATION IN THE RESPIRATORY SYSTEM OF RATS AT DIFFERENT AGES. K.J. Sullivan* and J.P. Mortola. Dept. of Physiology, McGill University, Montreal, Quebec, Canada, H3G 1Y6.

The viscoelastic properties of the lung may contribute to the difference observed between static and dynamic compliance in the newborn lung. In this study, the viscoelastic property of the respiratory system was examined in rats of different ages. The animals were divided into three groups; 0-1 day old (GPI, n = 6); 4-5 days old (GPII, n = 7) and 30-40 days old (GPIII, n = 8). Each animal was anaesthetized with sodium pentobarbital and a tracheal cannula was inserted. The animal was placed inside a fluid filled plethysmograph with the tracheal cannula projecting through the wall of the plethysmograph. Transrespiratory pressure at mid-thoracic level was set at atmospheric. Lung volume was then abruptly increased by rapidly withdrawing fluid from the plethysmograph. Following the volume step, lung volume is maintained constant and changes in transrespiratory pressure are recorded for 30 s. The rate of stress relaxation was obtained by calculating the slope (S) of the percent change in transrespiratory pressure per unit of time on a semi-log plot. GPIII rats exhibited the slowest relaxation (S = -6.7 ± 0.4 S.D.) whereas GPII rats demonstrated the fastest rate (S = -9.2 ± 1.0 S.D.). Stress relaxation in GPI rats was intermediate (S = -7.6 ± 0.5 S.D.) ($p < 0.01$). We conclude that the greater rate of relaxation in the newborn may contribute to the reduction in dynamic compliance.
(Supported by the Medical Research Council of Canada).

PULMONARY EPITHELIAL FUNCTION

55.1

Cigarette Smoke Exposure Increases Alveolar Permeability in Rabbits. M. Witten, R. Lemen, S. Quan*, R. Sobonya*, H. Roseberry*, J. Stevenson*, & J. Clayton*. Univ. of Arizona Health Sciences Center, Tucson, AZ 85724.

Cigarette smoke exposure (CSE) increases alveolar permeability in guinea pigs and humans; however, the mechanisms of this effect are unclear. We measured lung clearance of aerosolized technetium-labelled diethylenetriamine pentacetic acid as an index of alveolar epithelial permeability in rabbits exposed to cigarette smoke. Eighteen anesthetized and mechanically ventilated rabbits were assigned to 3 equal size groups; control (C), all smoke exposure (ASE), and a limited smoke exposure (LSE). Cigarette or sham smoke was delivered by syringe in a series of 5,10,20, and 30 breaths with a 20 min. counting period between each set of breaths. We observed a significant difference ($p<.05$) at 20 and 30 breaths between the C and ASE group values (% baseline) of T1/2, arterial blood pressure, and peak airway pressure. Carboxyhemoglobin was significantly different between the two groups at all exposure levels. Light and electron microscopic studies showed lung edema in the ASE group but normal intercellular junctions. We conclude that (1) CSE increases alveolar permeability (2) is associated with lung edema and (3) is not associated with disruption of the alveolar-capillary membrane. Supported by HL-07249 and BSRG 2 S07 RR0 S675-16 grants.

55.2

EFFECT OF OZONE (O_3) ON AIRWAYS EPITHELIAL PERMEABILITY TO POLAR SOLUTES: DEMONSTRATION OF ADAPTATION FOLLOWING REPEATED EXPOSURE. P.A. Bromberg, M. Ivanick* and V. Ranga, University of North Carolina, Chapel Hill, N.C. 27514.

Certain acute airways responses to O_3 inhalation diminish following repeated relatively brief daily exposures for 3 or 4 days. This phenomenon has been termed "adaptation." We have investigated whether the acutely increased airway epithelial permeability to polar solutes following O_3 exposure also shows adaptation. Guinea pigs (n=54) were studied immediately either after a single 3-hour exposure to 1 ppm O_3 or after the last of 4 such exposures on successive days. Animals were anesthesized and instilled intratracheally with 0.2 ml buffered saline containing ^{14}C-mannitol, ^{111}In-disodium pentetate, ^{3}H-inulin and ^{125}I-horseradish peroxidase as permeability probes. Five blood samples were collected over 30 minutes following instillation and analysed for probe appearance rates as an index of uptake. As compared to sham (air)-exposed controls, animals studied immediately after a single exposure showed the expected 2-4 fold increase in plasma appearance rates of all four probes. By contrast, immediately following the last of the 4 repeated daily O_3 exposures, no significant increase in probe uptake rates was found. We conclude that the O_3-induced acute changes in airways epithelial barrier function exhibit adaptation with a time course comparable to that observed for other airways responses.(supported by HEI 83-11, HL 29222 & CR807392 USEPA)

55.3

ALBUMIN TRANSPORT ACROSS EXCISED GUINEA PIG TRACHEA. V. Ranga, M. Ivanick*, D.W. Powell, J.T. Gatzy and P.A. Bromberg, University of North Carolina, Chapel Hill, N.C. 27514.

The permeability of excised guinea pig lower trachea to hydrophilic polar solutes was studied in open-circuited tubular flux chambers at 36°C. The steady state solute permeability coefficients (P) are tabulated (mean ± SE).

Solute	Molecular radius	P solute (x10^{-7}cm/sec) m→s	s→m	2p
^{14}C-mannitol	4Å	5.08±0.50	4.81±0.66	NS
^{3}H-inulin	14Å	0.91±0.17	0.87±0.19	NS
^{3}H-dextran	16Å	0.60±0.09	0.47±0.06	NS
^{125}I-albumin	36Å	0.43±0.12	0.09±0.01	<0.01
^{14}C-dextran	38Å	0.15±0.05	0.08±0.01	NS

Pore analysis of the serosa → mucosa (s→m) data is compatible with pores with a mean radius of about 98Å. It is comparable to those estimated from in vivo guinea pig airway studies (~70Å) and canine airway epithelia in vitro, but are much larger than the 10Å radius reported for the dominant pore population of the bullfrog alveolar epithelium. Only albumin (bovine serum) fluxes were asymmetric. This asymmetry can be attributed to the transepithelial potential difference (8.5 mV, lumen negative) and the high net negative charge on albumin at pH 7.4.(supported by HL 29222 and HEI 83-11)

55.4

NASAL ELECTRIC POTENTIAL DIFFERENCE AND RESPONSE TO AMILORIDE SUPERFUSION IN NEONATES. C.W. Gowen, Jr*, J. Gingras-Leatherman*, E.E. Lawson, R.C. Boucher*, M.R. Knowles*. The University of North Carolina, Chapel Hill, NC 27514.

The pulmonary epithelium secretes Cl^- as a driving force to form lung fluid during fetal life. However, net ion flux across pulmonary epithelium changes after birth from Cl^- secretion to Na^+ absorption. To evaluate this transition of function, we measured the potential difference (PD) across the nasal epithelium of healthy term infants (39.8±.2wks) and preterm infants (28.5±.9wks) with respiratory distress (RDS) during the first 72 hours of life. The PD and the PD response to superfusion with 10^{-3}M amiloride (Am), a Na^+ blocker, was recorded between a Ringer perfused bridge placed on the nasal mucosa and a reference electrode in the subcutaneous space. PDs (mean±SEM) measured in the first 24 hours were:

	N	mean PD(mV)	maxPD(mV)	Am inhibition
Term Infants	11	15.3±1.5	23.9±2.1	40.1±5.0%
Preterm Infants	6	9.5±0.8	16.3±0.8	33.5±5.7%

The basal PDs and the response to Am were unchanged over 72hr. Max PDs were lower when compared to older children (3-36m; 31.8±1.6mV; n=5) and both mean and max PDs were lower compared to young adults (21.0±.8mV, 31.6±.8mV; n=90). Am inhibition in children and adults (47.6±.9%) tended to be greater than term infants. We conclude that 1) nasal PD is lower in term infants than young adults, 2) Na^+ absorption contributes to the PD in the early postnatal period, and 3) RDS infants appear to have a lower PD than term infants.

55.5

CHARACTERIZATION OF α-ADRENERGIC RECEPTORS OF CAT TRACHEAL GLAND CELLS. David J. Culp*, and Matthew G. Marin. Univ. of Rochester, Rochester, New York 14642.

Airway secretions are derived primarily from submucosal glands. Evidence from studies of whole trachea suggests an α-adrenergic control of glandular secretion. We used gland cells (serous and mucous cells) isolated from cat trachea to identify and characterize glandular α-adrenergic receptors. In pharmacological studies, O_2 consumption was increased 69±7% (±SE, n=12) by phenylephrine (100 μM). Phenylephrine stimulation was dose dependent with an apparent equilibrium dissociation constant (K_D) of 7 μM (n=3). Phentolamine (5 μM) shifted the curve to the right (K_D = 200 nM). Atropine (10 μM) failed to inhibit phenylephrine-stimulated O_2 consumption. To further characterize gland cell receptors, we studied binding of the α-adrenergic antagonist, ^{3}H-dihydroergocryptine (DHE), to cell homogenates. Specific DHE-binding was saturable and to a single class of high affinity receptors (K_D = 4.6 nM, n=3). Maximal binding was 30 fmole/10^6 cell or about 19,000 sites/cell. DHE-binding was displaced by phentolamine (K_D = 42 nM), (-) epinephrine (K_D = 1.8 μM), (-) phenylephrine (K_D = 7.7 μM) and (-) isoproterenol (K_D = 140 μM). Binding was not inhibited by muscarinic and nicotinic cholinergic agonists or antagonists. The association (k_{+1}) and dissociation (k_{-1}) rate contants for DHE-binding to gland cell receptors was $2.1 \times 10^7 M^{-1} \cdot min^{-1}$ and 0.093 min^{-1}, respectively. This study confirms tracheal gland cells have high affinity α-adrenergic receptors.

55.6

EPINEPHRINE RESPONSE IN ISOLATED RABBIT TRACHEAL EPITHELIAL CELLS. Carole M. Liedtke. Case Western Res. Univ., Cleveland, OH 44106

Epinephrine (EPI) and isoproterenol (ISO) have previously been shown to increase cAMP levels in isolated rabbit tracheal epithelial cells (tracheocytes) with EC50s of 0.1 and 0.8 uM, respectively (Am. J. Physiol., in press). The response to EPI was further studied to explain the discrepancy in EC50 values between EPI and ISO. The β-adrenergic antagonist propranolol (20 μM) blocked the EPI response; however, a residual increased cAMP level persisted, suggesting the contribution of a non-β-adrenergic mediated increase in cAMP levels. To determine whether prostaglandins (PG) may contribute to the EPI response, cyclooxygenase inhibitors were tested for their ability to antagonize the EPI effect. Indomethacin, ibuprofen and acetylsalicylic acid increased the EC50 for EPI to about that for ISO (see Table). A role for the α-adrenergic receptor was suggested by the ability of phentolamine, an α-adrenergic antagonist, to increase the EC50 for EPI. The results suggest that an α-adrenergic receptor mediated PG release by rabbit tracheocytes may contribute to the biochemcial response to EPI.

ADDITIVE	CONC.	EC50 for EPI
Indomethacin	20 μM	1.0 μM
Ibuprofen	20 μM	1.2 μM
Acetylsalicylic acid	1 mM	0.7 μM
Phentolamine	20 μM	0.7 μM

Supported by NIH (HL 27700) and the Cystic Fibrosis Fouccation, Rainbow Chapter.

55.7

SUBSTANCE P (SP) AND VASOACTIVE INTESTINAL PEPTIDE (VIP) STIMULATE ACINAR CELL DEGRANULATION IN FERRET TRACHEA. A.A. Gashi*, D.B. Borson, C.B. Basbaum, and J.A. Nadel. Cardiovascular Research Institute, UCSF, San Francisco, CA 94143.

Previous work has shown that SP and VIP release macromolecules from tracheal explants (Baker ARRD 115:811; Peatfield ARRD 128:89). To determine which cells respond to these peptides, we studied peptide-induced changes in gland morphology accompanying release of $^{35}SO_4$-labeled macromolecules from tracheal explants. We anesthetized adult male ferrets with sodium pentobarbital. After 3 h, we excised the trachea and cut it into 5 pieces. We fixed one immediately and incubated the others for 1 h in 10 ml Ham's F12 medium, equilibrated with 95% O_2-5% CO_2, and containing 1 mCi $^{35}SO_4$. We washed the tissues every ½ h for 4½ h, and then incubated them for an additional ½ h in either F12 alone or F12 containing either bethanechol (10^{-5}M), SP (10^{-5}M), or VIP (2×10^{-6}M). The drugs increased secretion by 137±38 %, 126±21 %, and 171±36 %, respectively (mean ± SEM; $p < 0.01$, n=5). Light and electron microscopy of control tissues showed glands with narrow lumens. Serous and mucous cells were not degranulated or vacuolated. Glands treated with drugs had enlarged lumens, and serous and mucous cells were markedly degranulated. In other tissues, atropine, phentolamine, propranolol and tetrodotoxin did not prevent peptide-induced responses. These results suggest that SP and VIP act directly on acinar cells to cause gland secretion. (Supported in part by USPHS NIH Grant #HL-24136, and a grant from the Parker B. Francis Foundation).

56.1

ELECTRICAL STIMULATION OF THE HEPATIC VAGUS NERVE INDUCES AND SUPPRESSES GASTRIC CONTRACTIONS. K. C. Lee*. (SPON: D. C. Randall) Dept of Pharmacology, Univ. of Ky, KY 40536

We confirmed that electrical stimulation (S) of the hepatic afferent nerves induces gastric contractions (GC). We found that S can also suppress GC. GC were measured via an intragastric balloon in SD rats (~325g). An electrode was put on the cranial end of the hepatic branch of the vagus. S (sq. waves of 4Vx.7msec; 30sec) induced GC with amplitude related to the S frequency as reported (Sakaguchi, Experi. 37, 1981). When the balloon was inflated until the stomach began to contract (basal GC), GC were suppressed by a 6-min S (8Hz) as shown below: (X±SD; n=5; *, signif. dif. from pre-S at P<.01):

	Pre-S	First 3min During S	Last 3min During S	Post-S
GC/3min	3.3±.3	0.1±.0*	0.0±.0*	3.5±.3

Basal GC were also suppressed by gastric-vagotomy, iv atropine, or they disappeared after 30-120min (dying out). Two min after they died out, S (30sec) induced GC with amplitude related to the S frequency as shown below: (X±SD; n=5; *, signif. dif. from 10Hz-S at P<.01.)

S Freq (Hz)	.1	1	2	4	8	10
GC Amplitude (%)	0±0*	16±10*	25±12*	50±12*	105±22	100±0

S-induced GC were also eliminated by either gastric-vagotomy or iv atropine. These studies indicated that S of hepatic afferent nerves can induce or suppress vagal-muscarinic mediated GC.

56.2

EFFECT OF GLUCOSE ON INTESTINAL MOTILITY, TONE, LYMPH FLOW, AND FLUID ABSORPTION IN THE RAT. Jui S. Lee Department of Physiology, Univ. of Minnesota, Minneapolis, MN 55455.

The effect of glucose on motility, tone, lymph flow (J_l), & fluid absorption rate (J_v) was studied with a jejunal segment (20 cm long) of the fasted rats under pentobarbital anesthesia by procedures as described previously (J. Physiol. 345:489,1983). J_v or J_l was increased to the same extent by the presence of either glucose or $NaHCO_3$ in the luminal fluid. A maximal increase in J_v & J_l was obtained when both glucose & $NaHCO_3$ were present associated with a large increase in motility but a decrease in tone. During absorption from Krebs-Ringer solution, J_v & J_l were 2.6±0.1 & 0.2±0.1 ml/segment/h, respectively, & J_l accounted for 8±1% of J_v (mean ± SE, n = 46). In the presence of glucose (56 mM), J_v & J_l increased by 78±9 & 434±90%, respectively, & J_l accounted for 30±2% of J_v (n=8). When plasma glucose concentration was increased to ~40 mM during i.v. infusion of glucose, or by i.m. injection of alloxan (100-150mg/kg), both J_v & J_l were similarly increased. Furthermore, when glucose (200mM) was present in the serosal bathing fluid, both J_v & J_l were also increased. It is concluded that: (1) glucose is not a physiologically inert substance; (2) the increase of J_v is not entirely due to glucose absorption process but could be due to the decrease of tone; & (3) the increase of J_l by glucose suggests a decrease of capillary permeability resulting in the decrease of the rate of fluid transfer into the venous system. Supported by NIH grant AM 18085.

56.3

DOES INDOMETHACIN AFFECT GASTRIC EMPTYING? Sidney Fink* and Tapan K. Chaudhuri, VA Medical Center, Hampton, Va. 23667

The prostaglandins (PGE) are commonly known to stimulate gastric emptying (GE). Thus the PGE synthesis inhibitors are expected to have opposite effect i.e. delay GE. We studied the effect of Indomethacin (IDM), a PGE synthesis inhibitor, on GE thinking that IDM (a widely prescribed medication in the elderly) if it indeed delays GE, may affect the absorption of concomitantly administered drugs e.g. digoxin, L-dopa. Ten men (aged 69-85 years) free of diabetes, gastrointestinal disease or surgery, and not on anticholinergic, psychotherapeutic drugs, aspirin or other PGE synthesis inhibitors during the study, were selected for this study. The protocol was approved by the institutional review board and all subjects signed an informed consent form. Following overnight fast, the subjects consumed (4 ml/Kg) a test meal (a mixture of 35 gm Carnation Instant Breakfast, 240 ml whole milk and 50 gm powdered eggs made up to 600 ml water) mixed with a radioactive marker (0.5-1.0 mCi Tc-99m sulfur colloid). The GE half-time ($GET_{½}$) was determined using a gamma camera interfaced with a computer. A three series test of GE was determined on each subject over a week period - basal, post-placebo, and post-IDM (50 mg TID x 3 days). The data showed no significant difference (as evidenced by Friedman ANOVA and Wilcoxon sign tests) in $GET_{½}$ between basal (60 ± 20.5 min), post-placebo (68 ± 28.6 min) and post-IDM (60 ± 24 min) states. In conclusion IDM does not delay GE at least with the dose prescribed and at least in elderly men.

56.4

EXCHANGE DIFFUSION AND NON-ACIDIC CHLORIDE TRANSPORT IN BULLFROG GASTRIC MUCOSA. J.B. Matthews* P.K. Rangachari* P.H. Rowe* M. Starlinger*and W. Silen. Departments of Surgery, Harvard Medical School and Beth Israel Hospital, Boston, MA 02215

Exchange diffusion of Cl^- in non-secreting gastric mucosa was estimated by the decrement in short-circuited J_{Cl} from nutrient (N) to secretory (S) solutions replacement of luminal Cl^- with isethionate (Ise^-). In metiamide treated fundus J_{Cl} decreased from 7.12 ± 0.96 μEq/cm²/hr to 4.34 ± 0.54 (39 ± 5%, n=6) following Ise^- replacement for Cl^- in S. In antrum, J_{Cl} fell from 2.85 ± 0.32 to 1.80 ± 0.24 (37 ± 7%, n=5). Na^+ free N drastically reduced J_{Cl} to 1.34 ± 0.33, and on subsequent switch to Ise^- in S J_{Cl} was 1.41 ± 0.39 (net gain 5 ± 4%, n=5). With HCO_3^- free N J_{Cl} fell from 2.20 ± 0.32 to 1.49 ± 0.03 (31 ± 11%, n=4) with Ise^- in S. Respiratory acidosis (90% O_2-10% CO_2) and anoxia (95% N_2-5% CO_2) decreased J_{Cl} but the trans-effect was 41 ± 8% (n=4) and 29 ± 5% (n=4) respectively. Respiratory acidosis + anoxia (90% N_2-10% CO_2) eliminated the trans-effect, as J_{Cl} was 2.71 ± 0.47 with Cl^- in S and 2.54 ± 0.80 with ise^- (n=6). Ise^- substitution for Cl^- in S induced a large increase in PD and R whereas NO_3^- substitution in S had negligible effects, but NO_3^- in S decreased J_{Cl} by 42 ± 7%, suggesting that anion selectivity for exchange and passive conductance differ markedly. The similar trans-effect in non-secreting fundus and antrum suggests that exchange diffusion is a property of surface cells. Na^+ but not HCO_3^- in N was required for the trans-effect.

56.5

EFFECTS OF ASPIRIN (ASA) AND SODIUM SALICYLATE (SA) ON PROSTAGLANDIN (PG) SYNTHESIS IN AMPHIBIAN GASTRIC MUCOSA. P.H. Rowe*, G. Marrone*, M.J. Starlinger*, L. Trencis*, W. Silen. Departments of Surgery, Harvard Medical School and Beth Israel Hospital, Boston, MA 02215

Inhibition of PG synthesis is thought to be an important factor in NSAI induced ulcerogenesis. We investigated the electrophysiologic and morphologic changes, and the effects on PG synthesis of a 60 min exposure of Ussing chambered bullfrog fundic mucosae to 20 mM ASA or 20 mM SA placed in luminal (L) or nutrient (N) solutions, pH_N 7.3, pH_L 3.0. ASA_L, SA_L, and SA_N but not ASA_N produced a sharp fall in PD, rise in R and inhibition of acid secretion. Histologically ASA_L and SA_L produced severe surface and oxyntic cell injury, SA_N caused extensive edema in the lamina propria and occasionally luminal extrusion of oxyntic cells; in contrast ASA_N produced no apparent injury. Both 20 mM ASA_L and ASA_N produced highly significant reductions in generation of PGE_2, $PGF_{2\alpha}$, 6 keto $PGF_{1\alpha}$, whereas SA_L and SA_N caused lesser reductions in $PGF_{2\alpha}$ but, no change from controls in PGE_2 or 6 keto $PGF_{1\alpha}$. We conclude 1. ASA_N and ASA_L inhibit PG synthesis; ASA_L, but not ASA_N produces morphologic injury of gastric mucosa. In contrast, both SA_N and SA_L are injurious to the mucosa with far less inhibition of PG synthesis. 2. These data suggest that inhibition of PG synthesis may not be the mechanism in NSAI induced ulcerogenesis.

56.6

INSTILLATION OF CONJUGATED BILE SALT AND PROSTAGLANDIN IN THE RAT STOMACH. T.J. Sernka and T.L. Means*. Program in Physiology, School of Medicine, Wright State University, Dayton, OH 45435.

To determine the effectiveness of the gastric cytoprotection afforded by prostaglandins against bile salt damage, the stomachs of anesthetized rats were exteriorized and cannulated for determination of potential difference (PD) and net acid output (H^+). The stomachs were successively instilled with acid buffer, 5 mM and 15 mM sodium taurocholate (NaTC) with or without 3.3×10^{-6}M 16,16-dimethyl prostaglandin E_2 ($dmPGE_2$). The control H^+ was 1.21 ± 0.10 (SEM) μEq/min and the control PD was -35.2 ± 1.9 mV. Five mM NaTC reduced H^+ by 37% and 15 mM NaTC abolished H^+ and lowered the PD 45%. The correlation coefficient for H^+ and PD was 0.979. With $dmPGE_2$ present in the instillate, H^+ was twice as large in the control period. Exposure to 5 mM NaTC reduced H^+ by 63% and eliminated the stimulatory effect of $dmPGE_2$; the PD fell by 9%. Subsequent exposure to 15 mM NaTC depressed H^+ by 90% and the PD by 16%. The correlation coefficient for H^+ and PD was 0.907. Analysis of variance indicated that $dmPGE_2$ significantly increased H^+ in the 20 min before and after exposure to 5 mM NaTC; the PD was unaffected throughout. These observations indicate that 1) prostaglandins stimulate rather than inhibit H^+ in vivo, and 2) prostaglandins do not protect against conjugated bile salt actions on the H^+ and PD of the stomach. It may be concluded that any physiological cytoprotection of the stomach provided by prostaglandins is non-ionic.

56.7

SELECTIVE DEPLETION OF GASTRIC MUCOSAL GLYCOPROTEINS DURING ULCEROGENESIS IN RAT STOMACHS. Bernt T. Walther, Hans-Kristian Bakke,* Robert Murison,* and Arnt Raae.* Departments of Biochemistry and Physiological Psychology, University of Bergen,PKI,5000 Bergen, NORWAY.

Immobilization stress in darkness induced multiple foci of gastric erosions and ulcers in the rat, in a time-dependent manner. We have analyzed the ulcerogenic process by quantitative assessments of the protein , glycoprotein, and total tissue mass of separate layers of the rat stomach wall. Detection of the individual molecular species of the major protein and glycoprotein classes was accomplished, after separation of such molecules by polyacrylamide gel electrophoresis, by staining with ammoniacal silver of glutaraldehyde-treated proteins and of periodate-oxidized glycoproteins.

Our results demonstrate few and minor quantitative changes in mucosal and non-mucosal gastric proteins during ulcerogenesis in the rat. However, wet weight of the mucosa but not of the non-mucosal stomach is reduced after 24 hour immobilization stress. This reduction isreflected in dramatically quantitative diminution in glycoprotein contents of rat mucosal stomach layers. Multiple molecular species are affected. Our data suggest glycoproteins prevent ulcers.

56.8

CHARACTERISTICS OF A NEW EMESIS-PRODUCING INTESTINAL FACTOR. R.K. Harding*, T.J. McDonald*, H. Hugenholtz* and J. Kucharczyk* (SPON: B. Korecky). Univ. of Ottawa, Ottawa, Ont., Canada K1H 8M5 and Univ. of Western Ontario.

Vomiting was noted following i.v. injection in dogs of a side-fraction of porcine intestinal extract obtained during the purification of secretin. In dogs, 1-4 bouts of productive emesis began within 3 min of a bolus i.v. injection of 25 µg/kg of impure active fraction. Except for the emetic episodes, injected dogs (N = 10) appeared normal. Domperidone (1 mg/kg s.c.) spiroperidol (0.1 mg/kg i.v.) or naloxone (0.1 mg/kg s.c.) pretreatment did not block the emetic response to 25 µg/kg of impure fraction. The activity was next found to elute during ion-exchange HPLC in a profile different from any peptide tested to-date. It has long been proposed that the area postrema (AP), a circumventricular structure located on the floor of the fourth ventricle, contains a chemoreceptor trigger zone which mediates vomiting caused by various stimuli. However few plausible endogenous emetic substances have been suggested. In our experiments, suprathreshold doses of impure active fraction did not cause emesis in dogs with discrete AP ablations. The anatomical location of the extraction site, the low threshold, and the necessary involvement of AP, support the notion that the active fraction contains an important endogenous mediator of the vomiting response.

56.9

EFFECT OF NICOTINE ON THE SYNTHESIS AND SECRETION OF PROTEINS IN ISOLATED RAT PANCREATIC ACINI. M.C. Geokas, M.A. Dubick, G.A. Davis* and A.P.N. Majumdar, Department of Medicine, VA Medical Center, Martinez, CA 94553

Cigarette smoking and more specifically, nicotine, is known to affect pancreatic secretion. The present investigation determines the in vitro effect of nicotine on dispersed acini with regard to protein synthesis and secretion. The secretion of amylase and trypsinogen from acini was greatly stimulated by 3-25 mM nicotine. With 12.5 mM of the compound it was increased by 95 and 400%, respectively, as compared to control. The time course release of the enzymes revealed that in the presence of nicotine trypsinogen to amylase ratio remained 2-3 fold elevated over that of the control. The nicotine-induced stimulation of the enzyme release could not be blocked by 2.5 mM cycloheximide. When isolated acini were incubated with ^{3}H-leucine in the presence of nicotine, the released proteins showed 4-fold higher radioactivity than in the control. Cycloheximide dramatically decreased this increment. The release of ^{3}H-pulse-labeled proteins from the acini was greatly accelerated by nicotine. It is concluded that nicotine stimulated the release of enzymes and other exportable proteins from acini in vitro, and is attributed to (a) the increased synthesis of exportable proteins (b) acceleration of the secretory process or (c) stimulation of both synthesis and secretion. Furthermore, nicotine induces a non-parallel secretion of trypsinogen and amylase from the isolated pancreatic acini.

56.10

EFFECT OF ACETALDEHYDE(ACT) ADMINISTRATION ON PROTEIN SECRETION FROM ISOLATED PANCREATIC ACINI IN RATS. A.P.N. Majumdar, G.A. Davis*, M.A. Dubick and M.C. Geokas, Department of Medicine, VA Medical Center, Martinez, CA-94553

Although the effect of ethanol on pancreatic exocrine function has been extensively investigated, little attention has been paid to its major metabolite, acetaldehyde(ACT). This investigation determines the effect of 10 days(i.p.) administration of ACT on protein synthesis and secretion in isolated pancreatic acini in vitro. In acini from ACT-treated rats, the basal release of amylase, trypsinogen and chymotrypsinogen was increased by 50-60%, compared to the saline control. Nicotine (5-25mM) produced a profound enchancement in the secretion of the same enzymes from acini of both saline- and ACT-treated rats, and in the latter group this was accompanied by a rise in LDH release. Secretin (1 µM), CCK-8 (1 nM) and carbachol (10 µM) either alone or together with nicotine (12.5mM) caused a marked stimulation in the release of digestive enzymes. The magnitude of stimulation by nicotine plus secretin and nicotine plus carbachol was found to be higher in acini from ACT-treated rats as compared with the controls. In acini from ACT-treated rats, the release of pulse-labeled proteins by nicotine and ^{3}H-leucine incorporation into total acinar proteins were decreased by 40-55%, compared to the controls. It is concluded that ACT administration in vivo causes (a) enhancement in basal release of digestive enzymes, (b) augmentation of CCK-, secretin-, carbachol- and nicotine-induced release of digestive enzymes, (c) inhibition of acinar protein synthesis.

60.1

ROLE OF LEUKOTRIENES IN ENDOTOXIN INDUCED PULMONARY HYPERTENSION AND CHANGES IN RESPIRATORY MECHANICS. T. Ahmed*, B. Marchette*, B. Weichman*, M.J. Robinson* and M. Corriss* (SPON: W.M. Abraham). Mt. Sinai Med. Ctr., Miami Beach, FL.

We investigated the role of leukotrienes in endotoxin-induced pulmonary hypertension and changes in lung mechanics. In 5 sheep, hemodynamic measurements were obtained for the calculation of pulmonary vascular resistance (PVR) along with measurements of pulmonary resistance (R_L), PaO_2 and white blood cell (WBC) count before and at predetermined times after a 10 min infusion of E. coli endotoxin (0.3 ug/Kg), without and with treatment with the leukotriene receptor antagonist FPL-57231. Endotoxin caused a biphasic response (i.e., phase I=0-1 hr, phase II=1.5-4 hrs), with an increase in PVR and R_L to 382% and 412% of baseline respectively, during phase I and a lesser increase of 180-228% of baseline during phase II. Mean PaO_2 decreased from 85 to 66 mmHg and WBC count decreased from 8600 to 2800/mm^3 during phase I. When FPL-57231 (1mg/Kg/min) was administered prior to and throughout phase I, the endotoxin-induced changes in R_L and PaO_2 were attenuated during both phases. FPL-57231 also attenuated the phase I increase in PVR: but this was followed by an exaggerated response of PVR during phase II. This phase II increase in PVR could be reversed by a 10 min infusion of FPL-57231. FPL-57231 had no effect on endotoxin-induced decrease in WBC. We conclude that leukotrienes play an important role in the endotoxin-induced changes in pulmonary circulation and airway mechanics.

60.2

PRESSURE-FLOW RELATIONSHIPS IN STEADY AND PULSATILE PERFUSION OF DOG LUNGS FOLLOWING INDOMETHACIN. J.C. Newell and M.L. Ellsworth, Rensselaer Polytechnic Inst., Troy, NY 12181.

We have previously shown that the mean perfusion pressure required for pulsatile perfusion of hypoxic dog lobes was less than the pressure required for perfusion by comparable steady flow.(JAP 53:1583) We now find that this phenomenon persists following inhibition of cyclooxygenase metabolism by indomethacin. Left lower lobes of 8 mongrel dogs were perfused in situ with autologous blood using a non-pulsatile roller pump and a piston-type pump providing pulsatile flow with a 5 ml stroke volume. At a mean flow of 250 ml/min, in normoxia mean perfusion pressure was 20.4 ± 2.7 (SEM) torr in steady flow and unchanged at 21.1 ± 2.9 torr in pulsatile flow. When 25 mg of indomethacin was added to the perfusion circuit to block cyclooxygenase, mean perfusion pressure rose significantly to 28.4 ± 3.3 torr in steady flow and to 29.5 ± 3.2 torr in pulsatile flow. When the gas ventilating the lobe was changed from 5% CO_2 in air to 3% O_2 /5% CO_2 in N_2, reducing PO_2 from 134 ± 9 torr to 35 ± 4 torr, perfusion pressure rose significantly to 41.5 ± 3.5 torr in steady flow but to only 38.6 ± 3.2 torr in pulsatile flow. We conclude that the significant difference between the pressures required for perfusion with steady and pulsatile flow is not due to the elaboration of products of cyclooxygenase metabolism such as prostacyclin.

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60.3

EVIDENCE FOR A PULMONARY MICROCIRCULATORY IMPEDIMENT CAUSING HYPOXEMIA IN HEALTHY EXERCISING HORSES John H. Boucher, Rheotech Labs, Silver Spring, Md.

Exercise-induced hypoxemia routinely occurs in healthy horses, but the mechanism is unknown. Iced blood samples obtained from 5 conditioned Thoroughbred racing horses before and after a short speed-running workout were examined within 2 hours. After exertion, electron microscopy showed the blood contained >50% hypovolumic echinocytes, an abnormal red cell (RBC); such echinocytes alter microrheological behavior under all flow conditions. Also, mean erythrocyte osmotic fragility, an index of RBC deformability, shifted toward greater fragility ($P<0.05$) indicating a reduced mean cellular surface area to volume ratio. The noted physical characteristics would reduce RBC fluidity and the echinocyte would function as a single-cell emboli impeding microcirculatory blood flow. Pulmonary hypertension (mean pulmonary artery pressure 90 mm Hg, Thomas et al., 1981), hypoxemia (PaO_2 62 mmHg, Bayly et al., 1983; and PaO_2 69 mmHg, Thornton et al, 1983), and a calculated 19% pulmonary a–v shunt (from Thornton et al., 1983 data) corroborates that a naturally-occurring pulmonary pathophysiological circulatory mechanism operates in healthy horses. Consequently, the preformance capacity of the athletic horse probably operates suboptimally. I hypothesize that echinocytosis is the cause.

60.4

RESPONSE OF HETEROGENEOUS PULMONARY ARTERY SEGMENTS TO ISOPROTERENOL: THE CRITICAL NEED TO NORMALIZE TENSION DATA. R.C.Kolbeck and W.A.Speir* Medical Coll GA, Augusta, GA 30912

Comparative studies of vascular smooth muscle reactivity to inotropic agents are meaningful only if tension data are normalized, as for example, for segmental weight, cross sectional area, or luminal diameter. The literature is unclear as to which method of data expression is most meaninful. This study was therefore, undertaken to examine reactivity of segments of rabbit pulmonary artery (PA) to the agonist isoproterenol and relate the tension data to several vessel parameters. PA cylinders (4mm long) were incubated for 1 hr under 1g tension at 37°C, pH 7.4. After preconstriction with histamine, maximal relaxation were obtained for main PA (4mm id), branch PA (2.5mm id), small PA (1mm id), and distal PA (.4mmid) The data are normalized for values expressed as 1) g tension (control), 2)g/wet wt, 3)g/mm id, 4)g/mm^2 longitudinal cross section area, and 5)g/mm^2 circumferential cross sectional area. The results indicate that interpretation of vascular tension data may be substantially influenced by the manner of normalization.

	MPA	BPA	SPA	DPA
1)	0.99	0.52	0.88	1.60
2)	0.07	0.12	0.74	2.92
3)	0.32	0.26	0.74	2.69
4)	0.32	0.34	0.91	2.42
5)	0.10	0.14	0.62	3.14

60.5

EFFECT OF HYDROSTATIC EDEMA ON VASCULAR COMPLIANCE IN DOG LUNGS. M. Julien*, T.S. Hakim, R. Vahi* and H.K. Chang. Meakins Christie Lab., McGill Univ., Montreal, Canada.

Changes in pulmonary vascular resistance with edema have been studied extensively, however, changes in vascular compliance have seldom been reported. In 6 in situ isolated left lower lobes (LLL) of dog lungs perfused with autologous blood, we determined the pulmonary vascular compliance (C) during control conditions (E_0), and after production of moderate (E_1) and severe (E_2) hydrostatic edema. LLL weight was continuously recorded using a force transducer and C was calculated as the slope of the linear regression line relating the immediate changes in weight (ΔW) to the changes in mean intravascular pressure (ΔP) with a stepwise increase in flow (5 points collected in less than 30 sec). Corrections were made for the small fluid filtration occurring during the 30 sec. The wet to dry weight ratio at E_2 was 8.6 ± 1.8. The mean values (± SD) of C during E_0, E_1, E_2 measured with intravascular pressure ranging between 15 and 22 mmHg were 0.33 ± 0.11, 0.37 ± 0.10 and 0.43 ± 0.11 g/mmHg respectively. Thus, with edema C tended to increase however the change was statistically not significant. We conclude that hydrostatic edema does not have a major effect on vascular compliance in the range of pressures studied. Supported by the Medical Research Council of Canada.

60.6

DETERMINANTS OF SHUNT FLOW IN CANINE GRANULOMATOUS LUNG DISEASE. L. Schulman, Y. Enson, Columbia University College of Physicians and Surgeons, New York, N.Y. 10032.

Hypoxic vasoconstriction is attenuated by vasodilator prostanoids in a canine model of diffuse granulomatous lung disease, so that hypoxia increases the perfusion of shunt pathways. We examine the determinants of baseline shunt flow (Qs/Qt) and of changes in shunt flow (ΔQs/Qt) during hypoxia. Thirteen dogs were studied one month after intravenous injection of complete Freund's adjuvant. Vasomotion in this preparation can be manifest as a pressor response or blood flow redistribution or both. The vigor of pressor response was assessed as change in the difference between pulmonary arterial diastolic and mean wedge pressure (ΔPDG), while redistribution of blood flow between normal and diseased regions was evaluated with measurement of Qs/Qt using a continuous infusion of sulfur hexafluoride. At FIO2 0.10, PDG rose from 5±3 to 8±3 torr and Qs/Qt increased from 12±7 to 24±15 ($p<0.01$ for each), while cardiac output (CO) and heart rate did not change. The severity of disease, assessed by the lung weight/body weight (LW/BW) ratio, varied from 1.4 - 3.2% (normal 0.9%). Qs/Qt varied linearly with the LW/BW ratio ($n=13$, $r=0.70$, $p<0.01$), but not with heart rate, CO, $P_{\bar{v}}O2$, left atrial pressure or PDG. ΔQs/Qt varied with the LW/BW ratio ($r=0.73$, $p<0.01$) but with none of the other variables. In this model, the major determinant of Qs/Qt and ΔQs/Qt is the extent of the disease itself. Qs/Qt seems independent of the intrinsic vigor of pressor response in the pulmonary vascular bed.

60.7

A COMPUTER SIMULATION STUDY OF THE EFFECT OF EXTRA-ORGAN CAPACITANCE ON ISOGRAVIMETRIC BLOOD PRESSURE DETERMINATIONS. Kermit A. Gaar, Jr.; L.S.U. School of Medicine in Shreveport

Since all weight changes are the result of fluid that enters or exits the lung during isogravimetric measurements, a microcomputer simulation study was undertaken to investigate the effect that varying the size of the extra-organ capacitance might have on estimates of capillary pressure. For this purpose, a program for the model of the isolated perfused dog lung, consisting of a transcapillary fluid dynamics section and a hemodynamics section, was written in BASIC to be run on an Apple II+. In each simulated isogravimetric experiment blood flow was lowered in steps, and an attempt was made to determine capillary pressure by following organ weight changes while making adjustments to the height of the venous blood reservoir that caused the venous back pressure to vary. When the isogravimetric capillary pressure was believed to have been found, the simulation was ended. Following this, the true capillary pressure was revealed, which could then be compared with the isogravimetric estimate that had been obtained experimentally. To vary the amount of extra-organ capacitance in the perfusion system, 4 different sizes of venous reservoir were studied. Since the reservoir capacitance varies with the (tubular) diameter only, the diameters used were 0.5, 1, 2 and 4 cm. In general, it was found that the smaller sizes of reservoir gave the most accurate estimates of capillary pressure, and that excess capacitance in the perfusing system tends to degrade the accuracy of isogravimetric pressure measurements.

60.8

MECHANISM OF INCREASED RIGHT DUCT LYMPH FLOW FOLLOWING HYPOXIA. Ronald J. Torry* and Chandra M. Banerjee. Southern Illinois University School of Medicine, Carbondale, IL 62901.

Hypoxia increases the right duct lymph flow (RDLF) in various animals including dogs. Liberation of prostaglandin-like substances following alveolar hypoxia in cats (Science 185, 1974) and liberation of β endorphins both in acute hypoxia and in pulmonary edema in sheep (Endocrinology 108, 1981 and Fed. Proc. 41, 1982) have been reported. We explored the role of prostaglandins and endorphins in the causation of increased RDLF following hypoxia in dogs. The dogs were anesthetized with Nembutal (30 mg/Kg. IV) and were breathing room air with the aid of a ventilator. The RDLF values were obtained by direct cannulations. Additional values obtained were the respiratory gas tensions, pH, pulmonary artery pressure, left atrial and systemic blood pressures. The dogs were then allowed to breathe a hypoxic gas mixture (12% O_2). All the above parameters were again taken. Hypoxia resulted in an 87.5% increase in RDLF compared to control (control mean = 2.56 ml/hr; hypoxia mean = 4.88 ml/hr). The dogs were then treated either with Indomethacin (IV 5 mg/Kg) or with Naloxone (IV 10 mg/Kg). Both treatments along with hypoxia resulted in a decrease in RDLF compared to hypoxic control values. We conclude that the increase of both prostaglandin and endorphins play important roles as mediators in the causation of increased RDLF during hypoxia.

60.9

ENDOTHELIAL MEMBRANE MODEL SYSTEM TO STUDY TRANSPORT FUNCTION. F.M. Booyse*, M. Grover*, D. Dolenak*, J. Scheinbucks*, and J.P. Szidon. Michael Reese Hospital, Chicago, IL 60616

The quantitative study of transport functions of endothelium would be made easier by the availability of a reproducible in vitro model of the capillary wall. We report preliminary data on such a system using a novel approach to create an endothelial membrane. A Teflon mesh of 74 microns grid size separating two compartments was treated with Triton 80, saturated with thrombin (20 U/ml) and immersed in a 1:1 fibrinogen-fibronectin solution (.5-2.0 mg/ml). The resulting fibronectin-containing fibrin clot became firmly anchored to the Teflon mesh by intertwining its filaments. Endothelial cells (EC)(umbelical vein, pig's lung) were readily grown to confluency on this membrane and showed no tendency to detach. EC were characterized by ultrastructural properties factor VIII-related antigen and typical "cobblestone" tight packing. ^{3}H-H_2O introduced to one compartment equilibrated in approximately 120 min across the acellular Teflon-fibrin membrane. The addition of the EC monolayer caused no detectable delay in equilibration times. The acellular Teflon-fibrin membrane permitted the diffusion of an array of ^{125}I labeled tracer proteins (M_r 20-200K). Equilibrium was not reached in 5 hrs. The addition of the EC monolayer restricted proteins 45K and larger but allowed the passage of 29K. The system is reproducible, exhibits qualitatively transport properties of endothelium and is suitable for measurements of permeability coefficients and water flows.

60.10

EFFECT OF INTRACISTERNAL VERATRINE ADMINISTRATION ON LUNG FLUID BALANCE. M.B. Maron. Physiology Program, NE Ohio Univ. College of Medicine, Rootstown, Ohio 44272

In this study I evaluated the ability of an intracisternal injection of veratrine (a mixture of plant alkaloids) to produce pulmonary edema in chloralose-anesthetized dogs. 60 μg/kg veratrine was injected into the cisterna magna of 9 animals, and pulmonary vascular pressures were followed for 1 hr. Six dogs developed fulminant pulmonary edema after veratrine administration. In these animals, marked, but transient (avg 15 min) increases in systemic arterial (SAP, 263 ± 11 (SE) torr), pulmonary arterial (PAP, 83 ± 7 torr), and left ventricular end-diastolic pressures (LVEDP, 40 ± 9 torr) occurred, and large amounts of pink, frothy fluid, with protein concentrations ranging from 48-93% of plasma, appeared in the airways. At necropsy, the lungs exhibited a generalized consolidation and liver-like appearance, and post-mortem extravascular lung water (EVLW) content averaged 8.77 ± 0.41 g/g dry wt. Three animals escaped developing this massive degree of edema after veratrine (EVLW = 4.47 ± 0.31). These animals exhibited similar increases in SAP (260 ± 17 torr), but did not develop the degree of pulmonary hypertension (PAP = 52 ± 6 torr, LVEDP = 15 ± 2 torr) observed in the other group. These results suggest that both hemodynamic and permeability mechanisms may play a role in the development of this form of edema. It further appears that veratrine administration may provide a useful model of neurogenic pulmonary edema. (Sup by HL 31070)

60.11

BENZYL ALCOHOL-INDUCED CHANGES IN THE VASCULATURE OF ISOLATED DOG LUNGS. T. Izumi*, J. Gleisner*, and J. Hildebrandt. Virginia Mason Research Center, Seattle, WA 98101.

The effect of benzyl alcohol (BA), a commonly-used bacteriostatic agent, on the rate of weight gain ($\dot{W}$) and vascular resistance (R) was assessed using isolated lower lobes (n=22), perfused briefly with one or more of 1) autologous blood, 2) plasma, 3) blood containing BA, and 4) plasma containing BA. Filtration tests were performed after each perfusion by briefly increasing vascular pressure (Ppa=Pv) to 20 cm H_2O for 3 min with alveolar pressure=5 cmH_2O. $\dot{W}$ was calculated from the 3rd minute. All $\dot{W}$ were compared to a control filtration rate using blood (mean 1.75±0.43 (S.D.) gm min^{-1} 100 gm $lung^{-1}$). $\dot{W}$ was similar in blood- and plasma-perfused lobes (n=3). When BA was added to either perfusate, $\dot{W}$ increased progressively, particularly for plasma. Relative $\dot{W}$ are summarized below.

% B.A.	0.4%	0.7%	1.0%	1.3%
Blood	1.31±0.23(n=2)	1.62±0.15(n=5)	4.92±1.12(n=6)	4.96±1.29(n=2)
Plasma	3.07±0.48*(n=2)	27.44±5.60**(n=2)	138.56±62.80**(n=2)	

*=p<.05; **=p<.001 compared to reference (blood).

Mildly increased permeability was reversible by eluting BA, but severely altered permeability was not. Perfusion with 1.0% BA in plasma decreased R by about 50% (vasodilation), whereas 1.0% BA in blood sharply increased R more than 20 fold (probably microembolization). Since BA binds with albumin or red cell membrane (partition coefficient about 3 against saline) BA might similarly bind to Hb. Thus, the protection against severe BA-edema offered by blood might be explained by protein or membrane sequestration of BA, augmented by microvascular occlusion. Supported by HL 24163.

60.12

INFLUENCE OF MACROMOLECULAR CHARGE ON FLUID AND SOLUTE TRANSPORT IN THE LUNG. R. Winn, T. Izumi*, J. Gleisner*, E. Mansfield* and J. Hildebrandt. Virginia Mason Research Center, Seattle, WA 98101.

We investigated the role of albumin charge on the movement of fluid and solute. Transport was described by Kedem-Katchalsky equations with additional terms added to account for electroosmosis and electrodiffusion. In the first set of experiments, we looked for the development of differences in fluid filtration in isolated dog lobes. Flow through the endothelial barrier should produce a streaming potential, thus an electroosmotic pressure proportional to the charge of macromolecules in the vascular space. Therefore, solutions containing more negatively-charged macromolecules should result in less filtration. We found no difference in filtration between these solutions. In the second set, we examined the role of electrical charge in the transport of albumin across the pulmonary endothelial barrier of awake goats with chronic lymph fistulae. Two albumins with different charges and different fluorescent labels were infused and lymph-plasma ratios (C_L/C_P) along with C_L/C_P of endogenous albumin were measured 48 hrs later. C_L/C_P was smallest for the most negative molecules, however, the Stokes radius of these molecules was slightly larger. Comparison of the 3 C_L/C_P's with the 3 corresponding molecular sizes (gel column) allows size alone to explain the trend in difference. Also, theoretical considerations showed that size alone could explain the results. We conclude that no significant electrical potential develops in the lung and that molecular charge does not influence solute transport. (Supported by HL 24163, GM 29853 and GM 24990.)

VASCULAR SMOOTH MUSCLE AND ENDOTHELIAL CELL INTERACTIONS

61.1

PHASIC CONTRACTILE RESPONSES TO ALPHA-ADRENERGIC AGONISTS IN TAIL ARTERIES FROM SPONTANEOUSLY HYPERTENSIVE-STROKE PRONE RATS. J.H. Myers, F.S. Lamb*, and R.C. Webb, Department of Physiology, University of Michigan, Ann Arbor, Michigan 48109

This study characterizes contractile responses to α-adrenergic agonists in vascular smooth muscle from spontaneously hypertensive-stroke prone (SHR-sp) and Kyoto Wistar normotensive rats (WKY). Helical strips of tail arteries (art) were suspended in a muscle bath for measurement of isometric force generation. Addition of norepinephrine (NE) to the bath caused contraction in all strips. Art from WKY responded with an initial fast contraction followed by a tonic component. In contrast, contractile responses to NE in art from SHR-sp were characterized by an initial fast response followed by a phasic component. The magnitude (100-600 mg) and frequency (1-8 cycles/10 min) of phasic contractions varied directly with increasing concentrations of NE ($6x10^{-9}$ to $6x10^{-6}$M). Clonidine, guanabenz, phenylephrine and methoxamine also induced phasic activity in art from SHR-sp. The overall response was greatest with agents possessing a predominance of α_2 properties (i.e. clonidine greatest, methoxamine least). Phasic activity was blocked with yohimbine but not with prazosin. Contractions to 130mM KCl and 10^{-6}M angiotensin II were not phasic. These observations demonstrate a distinct functional individuality of vascular responses to α-adrenergic stimulation in SHR-sp which appears to be associated with the post-junctional alpha-2 adrenergic receptor.

61.2

POTENTIATION OF THE RESPONSES TO TRANSMURAL NERVE STIMULATION (TNS) BY EXOGENOUS ALPHA AGONISTS (AA) IN CANINE SAPHENOUS VEINS (CSV). M.P.J. Senaratne* & C.T. Kappagoda. Dept. of Medicine, Univ. of Alberta, Edmonton, Alberta, Canada T6G 2G3.

The present study was undertaken to assess the effects of exogenous AA on the effector response to TNS in CSV rings. The response to a fixed train (5 s duration) of TNS (8 Hz, 0.3 ms, 9 V) applied every 5 min was determined first. Once a stable response was established, the response to the same train of TNS was determined in the presence of sub-threshold (for contraction) concentrations of noradrenaline (NA), tyramine (Tyr), methoxamine (Meth) or clonidine (Clo), with each agonist added cumulatively to the tissue bath. The responses to TNS in the presence of NA were as follows (% control, mean ± SEM):

NA(log mol/l)	0(control)	-9.0	-8.5	-8.0	-7.5	-7.2
TNS	100	101±2	107±7	136±10	213±33	246±37

Tyr, Meth, and Clon too produced a similar concentration dependent potentiation of the response to TNS: maximum responses were 306±81, 353±68 and 384±79% (control) respectively. The present study indicates a potentiation of the effector responses to TNS by exogenous AA. This is likely to be mediated by a post-synaptic mechanism as it is present with methoxamine a relatively specific alpha$_1$ agonist which is also not a substrate for uptake$_1$. The study also suggests that, pre-synaptic alpha$_2$ inhibition is unlikely to be of any biological significance (with regards to the effector response) in the CSV during conditions similar to those of the present study.

61.3

ALPHA-ADRENERGIC COMPONENT OF MAXIMUM CORONARY VASCULAR CONSTRICTION Russell A. Bialecki* and George S. Malindzak, Jr. Physiology Department Northeastern Ohio Universities College of Medicine, Rootstown, Ohio 44272

The objective of this study was to determine the amount of alpha adrenergic-mediated (AAM) contraction which contributes to maximum coronary vascular contraction. Vascular loops (3.0 mm in length) of the left anterior descending coronary artery were harvested from the hearts of anesthetized mongrel dogs (n=10). The loops were (1) placed in 37°C baths of Krebs-Henseleit buffer with 10^{-7}M propranolol, (2) set to optimal resting length, and (3) challenged with maximal doses of 10^{-2}M $BACl_2$, 10^{-5}M norepinephrine (NE) and transmural electrical field stimulation (TES; 12v, 1.0msecm 1-1000Hz) in control, and adrenergically blocked (phentolamine; PHE) and reserpine (RES) treated loops. Maximum AAM active tension (74.87 ± 9.36 g/cm^2) was produced with 10^{-5}M NE (control). Equivalent responses were obtained with TES ≤ 60Hz and blocked with 10^{-5}M PHE or 10^{-3}M RES. Significantly greater ($p<0.01$) active tension was developed in response to $BACl_2$ (403.8±47.3 g/cm^2) and supramaximal TES (≤1000Hz; 396.9±44.1 g/cm^2). No significant difference was observed between the $BACl_2$ and the supramaximal TES responses. In conclusion, in isolated coronary arteries, (A) the maximum active tension developed by coronary vascular smooth muscle was approximately 400% of the AAM response, and (B) adrenergic-mediated responses were limited to TES of 60Hz or less. This work was supported in part by the American Heart Association.

61.4

THE RECEPTOR-RESERVE DETERMINES THE MODULATION BY COOLING OF ALPHA-ADRENERGIC RESPONSES IN CANINE CUTANEOUS VEINS. N.A. Flavahan* and P.M. Vanhoutte, Department of Physiology, Mayo Clinic, Rochester, MN 55905.

To determine the influence of the receptor-reserve in the modulation of adrenergic responses by cold, rings of canine saphenous veins were suspended for isometric force recording in physiological salt solution. Cooling (from 37° to 24°C) augmented contractions to norepinephrine under control conditions, following $alpha_1$-adrenoceptor blockade (prazosin), but not following $alpha_2$-adrenergic blockade (rauwolscine). Cooling augmented contractions evoked by the $alpha_2$-adrenergic agonists B-HT 920 and UK 14,304, did not affect responses to the full $alpha_1$-adrenergic agonist phenylephrine but virtually abolished those to the partial $alpha_1$-adrenergic agonist ST 587. Following partial, irreversible $alpha_1$-adrenergic blockade with phenoxybenzamine, cooling reduced the contractions evoked by phenylephrine and norepinephrine. These experiments indicate that: (a) cooling augments $alpha_2$-adrenergic but reduces $alpha_1$-adrenergic responsiveness in canine cutaneous veins; (b) under normal conditions the inhibitory effect of cold on $alpha_1$-adrenoceptors is buffered by the large $alpha_1$-adrenoceptor reserve, so that the potentiating effect of cold on the $alpha_2$-adrenergic component of the response to norepinephrine predominates. (Supported in part by NIH grant HL 05883.)

61.5

MUSCULAR AND ENDOTHELIAL RESPONSIVENESS TO $ALPHA_2$-ADRENERGIC ACTIVATION IN CANINE BLOOD VESSELS. V.M. Miller and P.M. Vanhoutte. Dept. Physiol., Mayo Clinic, Rochester, MN 55905.

$Alpha_2$-adrenoceptor stimulation can initiate endothelium-dependent relaxations of canine and porcine arteries (Cocks and Angus, Nature 305:627, 1983). The present study was designed to compare endothelial $alpha_2$-adrenoceptors in arteries and veins. Rings of canine femoral and pulmonary arteries and veins, with and without endothelium, were suspended for isometric force recording in physiological salt solution (95% O_2-5% CO_2; 37°C). In the presence of prazosin and propranolol, norepinephrine caused relaxations of all blood vessels during contractions evoked by prostaglandin $F_{2\alpha}$ or serotonin, provided the endothelium was present. These relaxations were blocked by rauwolscine and mimicked by the selective $alpha_2$-adrenergic agonist UK 14,304. The magnitude and duration of the inhibitions were least in the femoral vein and the pulmonary artery; these two vessels exhibited the strongest direct muscular response to $alpha_2$-adrenoceptor activation. These experiments indicate that: (a) $alpha_2$-adrenoceptors which mediate inhibition of vascular smooth muscle are present on the endothelium of arteries and veins, both in the systemic and pulmonary circulation; (b) the presence of muscular $alpha_2$-adrenoceptors masks endothelium-dependent responses to $alpha_2$-adrenoceptor agonists; and (c) the muscular $alpha_2$-adrenoceptors are more numerous in blood vessels chronically exposed to a low P_{O_2}. (Supported in part by grants HL 31183 and HL 07111.)

61.6

OXYTOCIN INDUCES ENDOTHELIUM-DEPENDENT RELAXATION OF CANINE BASILAR ARTERIES. Z. Katusic*, J.T. Shepherd and P.M. Vanhoutte, Dept. Physiol., Mayo Clinic, Rochester, MN 55905.

To determine how oxytocin affects endothelial cells and vascular smooth muscle, paired rings of canine basilar and femoral arteries were suspended for isometric force recording in organ chambers filled with physiological salt solution (95% O_2, 5% CO_2; 37°C). In one ring of each pair the endothelium was removed as demonstrated by the absence of the relaxation induced by thrombin (basilar arteries) or acetylcholine (femoral arteries). In basilar rings with endothelium, oxytocin caused concentration-dependent relaxations under basal conditions or during contractions evoked by prostaglandin $F_{2\alpha}$. Removal of the endothelium abolished the inhibitory response to oxytocin. In femoral arteries, with and without endothelium, oxytocin caused contractions. These effects of oxytocin were antagonized by the V_1-vasopressinergic antagonist $d(CH_2)_5$ Tyr(Me) AVP. These results suggest that activation of V_1-vasopressinergic receptors by oxytocin causes endothelium-dependent relaxations in basilar but not in femoral arteries. These studies suggest that oxytocin, like vasopressin, may favor the redistribution of blood flow from the peripheral to the cerebral circulation. (Supported in part by NIH grants HL 05883 and HL 31183.)

61.7

PLATELET ACTIVATING FACTOR INDUCES ENDOTHELIUM-INDEPENDENT RELAXATION OF ISOLATED CANINE BLOOD VESSELS. D.S. Houston* and P.M. Vanhoutte, Department of Physiology, Mayo Clinic, Rochester, MN 55905.

Platelet activating factor (PAF; 1-O-alkyl-2-acetyl-sn-glyceryl-3-phosphorylcholine), causes hypotension and vasodilatation in the rat. The present study was designed to determine the effects of PAF on isolated blood vessels. Rings of canine left circumflex coronary artery and femoral artery were suspended in aerated physiological salt solution for isometric tension recording. The intimal surface of some rings was rubbed; functional loss of endothelium was confirmed by absence of the characteristic relaxation to acetylcholine. Synthetic PAF caused a dose-dependent depression of intrinsic myogenic tone in coronary rings, but had no effect on quiescent femoral arteries. In coronary rings, contractions to prostaglandin $F_{2\alpha}$ were abolished by cumulative concentrations of PAF. Likewise, femoral artery rings contracted with norepinephrine or prostaglandin $F_{2\alpha}$ relaxed to PAF. There was no difference between rings with and without endothelium. The relaxations to PAF were not reversed by addition of propranolol but were reduced in the presence of indomethacin. These experiments demonstrate that in canine blood vessels, PAF causes relaxation of vascular smooth muscle independently of the endothelium. Products of the cyclo-oxygenase pathway may be involved in the inhibitory effect of PAF. (Supported in part by NIH grants HL 05883 and HL 31183.)

61.8

VASCULAR SMOOTH MUSCLE OXYGEN-DEPENDENT TENSION: POSSIBLE ROLE OF ENDOTHELIUM AND CYCLIC C-GMP. R.F.Coburn, R.Eppinger*, and D.E.Pew* , Univ. of Penn. Sch. of Med., Philad., Pa., 19104

Data in the literature suggest that O_2-dependent mechanical tension in VSM may require an intact endothelium. We studied effects of endothel. removal (rubbing technique) in rabbit thoracic aorta (RA) (5.5 uM norepi. contract.), and the neonatal ductus arteriosus of the guinea-pig and the lamb, on O_2-dependent tension. Rings were studied under isometric conditions in an organ bath. Carbamylcholine relax. which occur in end(+) preps. were absent in end(-) preps, and carb-induced c-GMP increases occurred in end(+) and did not occur in end(-) preps. Maximal tension changes due to decreasing PO_2 from approx. 200 to 20 mm Hg (given as % of active tension ± SD):

	Rabbit Aorta	Lamb Ductus	Guinea-pig Ductus
End(+)	86.4 ± 39.1 (N=7)	91.4 ± 10.2 (N=2)	85.5 ± 5.4 (N=2)
End(-)	61.3 ± 16.4	92.4 ± 8.3	88.6 ± 4.3

C-GMP levels, pmol/gram (wet), in RA freeze clamped during a maximal hypoxia relax. (MHR) and at 25-50% of maximum hypoxia-induced relax. (25-50%) (*$P< 0.025$):

	Control	MHR	25-50%
End(+)	6.1 ± 1.7 (N=7)	6.0 ± 1.5 (N=7)	3.9 ± 0.9* (N=7)
End(-)	3.5 ± 3.7	5.3 ± 3.7	

Nitroglycerine-induced relax. gave [c-GMP] increases from 6.8 ± 3.1 to 50.8 ± 37.5. We conclude that endothelium relaxing factors are not involved in O_2-dependent tension in these tissues.

62.1

RENAL HANDLING OF Na^+ IN HOMOZYGOTE AA AND HETEROZYGOTE AS NORMOTENSIVE NIGERIANS. P.E. IDAMOA* AND C.U. ERHUNSE* (SPON. A.B. EBRIGBE). University of Benin Teaching Hospital, P.M.B. 1111, Benin City, Nigeria.

Dahl and Hein, 1975 have reported inherited defects in renal Sodium excretion in experimental rats (Circ, Res. 36: 692). In order to assess renal handling of Na^+ in AA and AS subjects, 10 gms of extra table salt dissolved in a glass of water was taken every morning for three consecutive days. Urine was collected between 2130 hrs and 0630 hrs on each day and analysed for Na^+ and K^+. Haemoglobin genotypes were typed using a standard cellullose acetate paper electrophoesis. Out of 21 volunteers living under identical conditions, 18 subjects (10 AA, 7 AS and 1 SS) completed the study. The 10 AA (5 females and 2 males) (58.8%) were aged 17-24 yrs (mean age 18.1 yrs) and mean weight 60.8 kg. The 7 AS (5 females and 2 males) (41.2%) were aged 16-24 yrs (mean age 19.9 yrs) and mean weight 60.4 kg. Mean Na^+ excretion for AA was 69.3 mmol/9 hrs $\pm$ 13.4 (equivalent to 184.8 mmol/24 hrs) and 88.8 mmol/9 hrs $\pm$ 20.3 (equivalent to 236.8 mmol/24 hrs) for AS. Mean Na^+ excretion in AS was significantly higher than that in AA ($P<0.025$). Mean K^+ excretion for AA was 23.4 mmol/ hrs $\pm$ 7.2 (equivalent to 62.4 mmol/24 hrs) and mean K^+ excretion for AS was 18.9 mmol/9 hrs $\pm$ 4.7, (equivalent to 50.4 mmol/24 hrs). The difference in K^+ excretion was not statistically significant. This study has shown a higher Na^+ excretion in AS subjects, a possible indication of a protective genetic mechanism against hypertension in AS subjects.

62.2

REDUCED ROLE OF CARDIOPULMONARY RECEPTORS IN MODULATION OF CAROTID SINUS REFLEXES IN SODIUM LOADED DOGS. A. Tramposch,* K.B. Brosnihan and C.M. Ferrario, Dept. of Cardiovascular Research, Cleveland Clinic, Cleveland, OH 44106.

To obtain further evidence that changes in sodium (Na) balance affect the interplay between the sympathetic nervous system and baroreceptor reflexes, four mongrel dogs received a continuous intravenous (IV) infusion of a sodium chloride (NaCl) solution (13 mEq Na^+/hr) for 14 days. They were then anesthetized with morphine-chloralose and following removal of both aortic depressor nerves and one carotid sinus (CS), hemodynamic responses to occlusion of a remaining CS were determined before and after parasympathetic blockade with atropine and following section of the vagus nerve. Compared to control dogs the increases in mean arterial pressure (MAP) due to occlusion of a CS were twice as large in sodium loaded animals (SL). The potentiation of the pressor response was due to a larger increase in peripheral resistance since rises in cardiac output were about the same in both groups. In SL dogs section of the vagus nerve, after pretreatment with atropine (0.13 mg/kg IV), did not produce any further enhancement of the pressor response to carotid sinus hypotension; however, in control dogs peak responses to CS occlusion were increased after vagotomy. These data suggest that high Na^+ intake enhances sympathetically mediated reflexes by a mechanism which in part may depend upon blunting of the activity of cardiopulmonary receptors. (Supported by NHLBI grant HL-6835).

62.3

EFFECT OF SELECTIVE SODIUM DEPLETION IN BLOOD PRESSURE IN UNINEPHRECTOMIZED (UNx) RATS. C. E. Ott, B. J. Holtzclaw*, J. H. Downs* and T. A. Kotchen*. University of Kentucky, Lexington, KY 40536.

It has been shown that selective Na loading, without Cl prevents the rise in blood pressure (BP) seen in the Dahl-S rat when both Na and Cl are present. It has also been found that NaCl, but not $NaHCO_3$, increases BP in Doc-salt hypertension. Thus it is possible that Cl as well as Na might be important in BP regulation. This study determined if low Na in the absence of low Cl altered BP in the UNx rat. Two groups of 8 rats underwent UNx and were then fed a low NaCl diet or a low Na, normal Cl diet. Systolic BP was measured by tail cuff for 1 week before and 3 weeks after UNx. Baseline BP was no different between the two groups (124.3$\pm$2.2 vs 123.9+2.6 mmHg). Seven days after beginning the diets the BP was higher in the low Na group than the normal Cl group (137.4+3.5 vs 127.0$\pm$3.8; $p<.001$). After 3 weeks on the diets, BP of the low NaCl group returned to baseline while the normal Cl group was significantly higher ($p<.05$). Despite similar Na depletion, plasma renin activity (PRA) was significantly decreased in the normal Cl group compared to the low NaCl group (11.1$\pm$2.1 vs 25.8+3.1 ng/ml/hr, $p<.001$). The data are consistent with previous studies which suggest that 1) alterations in chloride intake as well as Na alter the time course and magnitude of BP chances, and 2) PRA is reduced by chloride intake despite concomitant Na restriction.

62.4

ATRIAL NATRIURETIC FACTOR (ANF) IN DAHL STRAIN OF HYPERTENSIVE (HT) AND NORMOTENSIVE (NT) RATS: EFFECTS OF DIETARY SALT. W.T. Link*, M.B. Pamnani, and F.J. Haddy. Department of Physiology, Uniformed Services University, Bethesda, MD 20814

We have reported increased levels of ANF in rats with reduced renal mass salt hypertension. We now report these studies in Dahl S and R rats. Atrial extracts (AE) were prepared from atria of S and R rats on high salt (HS) ($\overline{BP}$ 177±3 and 118±1 mmHg, respectively) and from S and R rats on low salt (LS) ($\overline{BP}$ 131±1 and 117±1 mmHg, respectively). 200 µl of AE was injected iv into anesthetized Sprague Dawley (SD) rats and its effect on excretion of urine volume (UV, µl/min) and sodium ($U_{Na}V$, µEq/min) were measured. The results were:

	UV by R	UV by S		$U_{Na}V$ by R	$U_{Na}V$ by S
LS	25.06±3.17	36.25±5.76	LS	2.63±0.50	4.84±0.88
HS	32.44±4.44	48.90±8.57	HS	3.53±0.82	6.45±1.44

Relative to AE from R rats, AE from S rats produced greater UV ($P<.05$) and $U_{Na}V$ ($P<.05$) regardless of salt intake and AE from S_{HS} rats produced greater UV ($P<.05$) and $U_{Na}V$ ($P<.05$) relative to AE from S_{LS} rats. In other experiments we injected iv 200 µl of AE from SD rats into NT S_{LS} and R_{LS} rats. Relative to R_{LS} rats, S_{LS} rats showed less UV (83.43±1 3.90 vs. 21.88± 4.80, $P<.05$) and $U_{Na}V$ (9.96±2.05 vs. 2.40±2.08, $P<.05$). These studies show that S rat atria contain more ANF than R rat atria and S is less sensitive to ANF from SD, confirming the results of Hirata et al. In addition they show that HS increased ANF in S. Increased ANF in S rats may be related to their decreased sensitivity to ANF.

62.5

THE NA^+-PUMP AND NA^+-K^+ PERMEABILITIES OF SHR CULTURED VASCULAR SMOOTH MUSCLE CELLS (VSMC). L.Hopp*, H.Tamura*, M.Kino*, A.Tokushige*,and A.Aviv. NJ Med. School,Hypertension Research Unit, Newark, NJ 07103

To explore the membrane abnormalities of genetically transmitted hypertension, intracellular Na^+ levels (Na^+_i), $^{86}Rb^+$ and $^{22}Na^+$ fluxes,and ^{3}H-ouabain binding studies were performed in serially passed cultured VSMC derived from SHR, Wistar Kyoto (WKY), and Wistar rats (W). We have found that: a)there was no difference in Na^+_i among the three groups, b)Rb^+ efflux and Na^+ influx rate constants of SHR were the highest among the three groups, c)ouabain-sensitive Rb^+ influx rate constant (per min;Mean±SEM) of SHR (.44±.08, n=64), was higher than that of WKY (.39± .05, n=60,$p<.01$), whereas it was not different from that of W (.45±.06, n=56), d)the number of ouabain binding sites per cell ($x10^5$) of SHR (3.00±.02,n = 231) and WKY (2.87±.05, n=245) were lower than those of W (3.62±.04, n=225, $p<.01$). These findings indicate that, among the three groups, SHR VSMC have the greatest membrane permeability to Na^+ and K^+, and the highest activity per unit Na^+-pump. Since these abnormalities are demonstrated in cultured cells,it can be concluded that SHR rat VSMC have innate defects in Na^+-K^+ homeostasis.

62.6

MECHANISMS OF NA+ EXTRUSION IN CULTURED SHR VASCULAR SMOOTH MUSCLE CELLS (VSMC). A.Tokushige*, M.Kino*, H.Tamura*, L. Hopp*, and A.Aviv. NJ Med. School, Hypertension Research Unit, Newark, NJ 07103

By measuring the Na^+ efflux rate (k_o) and influx rate (k_i) constants in Ca-deficient medium, we examined the relative contribution of the ouabain sensitive (OS) and the bumetanide sensitive (BS) Na^+ extrusion to Na^+ efflux in cultured VSMC of SHR, normotensive Wistar Kyoto (WKY) and Wistar (W) rats. The cells were preloaded with Na^+ to attain a maximal stimulation of the Na^+-pump. Results ($x10^{-2}$/min; Mean±SEM; number of observations indicated in brackets) are presented in the table. * and ** indicate significance at $p<.05$ and $<.01$ for SHR vs. W, whereas, ++ denote significance at $p<.01$ for SHR vs. WKY.

	SH	WKY	W
Total k_o	26.6±.33(90)	19.7±.57(85)++	25.8±.43(90)
BS k_o	6.6±.52(91)*	1.3±.57(88)++	4.6±.70(85)
OS k_o	13.4±.75(59)	10.9±.91(62)++	14.5±.64(63)
k_i	11.9±.65(65)**	5.3±.40(60)++	8.0±.36(60)
k_o/k_i	2.23±.12(65)**	3.72±.31(60)++	3.23±.16(60)

Coupled with our previous observation of lower Na^+-pump units in SHR as compared with W VSMC, these results indicate that VSMC's of the SHR manifest not only the highest Na^+-pump turnover rate,but also the highest BS k_o among the three groups. These findings probably reflect compensatory mechanisms for the higher Na^+ inward permeability of SHR cells. Moreover,the lowest k_o/k_i in the SHR group indicates a relatively reduced capacity for Na^+ extrusion.

62.7

MICROVASCULAR PERMEABILITY AND PRESSURE IN ISOLATED HINDQUARTERS OF SPONTANEOUSLY HYPERTENSIVE RATS. R.J. Korthuis*, M.I. Townsley*, and A.E. Taylor. Department of Physiology, University of South Alabama, Mobile, Alabama 36688.

The transvascular escape rate (TER) of labelled albumin is reported to increase in essential hypertension. However, the mechanism for this augmented rate of albumin efflux is uncertain and may be related to increased microvascular permeability or pressure or both. In order to determine the possible contributions of these mechanisms to increased TER of protein, the osmotic reflection coefficient for total plasma proteins and isogravimetric capillary pressure were estimated in isolated hindquarters of spontaneously hypertensive (SH), Wistar-Kyoto (WKY), and Wistar (WS) rats. Estimates of the reflection coefficient obtained SH, WKY, and WS were not significantly different ($p \geq 0.20$) averaging 0.86 ± 0.10, 0.93 ± 0.18, and 0.95 ± 0.08, respectively. However, isogravimetric capillary pressure was significantly greater in SH than in WKY or WS (12.0 ± 1.0 vs. 9.8 ± 0.8 vs. 10.3 ± 0.8 mm Hg, respectively). These results indicate that (1) skeletal muscle microvascular permeability to total plasma proteins is similar in SHR, WKY, and WS and (2) if TER for protein is elevated in hypertensive skeletal muscle, the primary mechanism for this process may be increased convective transport of protein secondary to elevated microvascular hydrostatic pressure. (This study was supported in part by NIH HL-22549).

62.8

ARTERIOLAR DIAMETER AND TISSUE BLOOD FLOW IN SUPERFUSED AND COVERED CREMASTER MUSCLE PREPARATIONS OF SPONTANEOUSLY HYPERTENSIVE (SHR) AND NORMOTENSIVE (WKY) RATS. J.H. Lombard, G.J. Smits*, and R.J. Roman. Dept. of Physiology, Med. Coll. Wisconsin, Milwaukee, WI 53226

In situ microcirculatory studies of skeletal muscle employ preparations which are either irrigated with physiological salt solution (PSS) or covered with plastic wrap or a cover slip. Differences in local tissue environment during such protocols could affect microvessel diameters and tissue blood flow. In these experiments, arteriolar diameters were measured in the cremaster muscle of 12-15 week old SHR and WKY while the preparation was first superfused with PSS equilibrated with 0% O_2-5% CO_2-95% N_2 for 90 minutes and then covered with a plastic sheet (Saran wrap). Skeletal muscle contraction and neurogenic arteriolar tone were blocked with 0.1 µg/ml tetrodotoxin. Tissue blood flow was assessed with a dual channel differential laser-Doppler flowmeter (Perimed). In the superfused cremaster muscle, arteriolar diameters and laser-Doppler flow (LDF) signals were similar in SHR and WKY. However after the preparation was covered, arteriolar diameters decreased more in SHR (-18±4.1 µm) than in WKY (-3±2.6 µm). LDF signal also decreased more in covered SHR preparations than in covered WKY preparations. These data suggest that experimental conditions can affect diameter and flow measurements during in situ studies of the microcirculation, and that measurements in hypertensive animals can be affected more than those in normotensive controls. (Supported by NIH #PO1 HL29587).

62.9

NON-INVASIVE BLOOD PRESSURE MEASUREMENT IN YUCATAN MINIATURE SWINE USING TAIL CUFF SPHYGMOMANOMETRY Catherine M. Cimini* and Edward J. Zambraski, Rutgers University, New Brunswick, N.J. 08903

A relatively new non-invasive photo-electric flow sensor and automated tail cuff pressure monitoring system (IITC, Landing, N.J.), designed for use with non-heated animals, was evaluated for its accuracy in measuring systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) in seven, 40-90 kg, conscious normotensive and hypertensive Yucatan miniature swine. Direct pressures were recorded from chronic arterial catheters for simultaneous comparisons with tail cuff pressure and tail blood flow recordings. Thirty-three tests, involving 144 pairs of measurements, were conducted. Over a blood pressure range of 60 to 202 mmHg, induced pharmacologically or due to DOCA hypertension, the directly measured SBP (151.7±5.6 mmHg) and tail cuff SBP (150.3±5.6 mmHg) were significantly correlated ($r=.96$, $P<0.01$). The average indirect DBP, (88.9±3.8 mmHg) was found to consistently underestimate measured DBP (106.9±3.6 mmHg) by approximately 15%, however, these two methods were significantly correlated ($r=.87$, $P<0.01$). Actual MAP and tail cuff MAP, 126.0±2.1 and 122.3±2.6 mmHg, respectively, differed by approximately 5% and were significantly correlated ($r=.72$, $P<0.01$). These results indicate that this system may be used in non-heated animals to accurately measure blood pressure in miniature swine.

62.10

NALOXONE FAILS TO RAISE BLOOD PRESSURE IN HEMORRHAGED RATS. Danley F.Brown* and Robert E. Burr* (SPON: J.P. Hannon). Letterman Army Institute of Research; San Francisco, CA 94129

Naloxone (NAL) has been reported to increase mean arterial pressure (MAP) in rats with hemorrhagic hypotension. We did a series of experiments to replicate the original experimental observations of this NAL effect (Faden and Holaday, Science 1979;205:317). One hundred and ninety-one male Sprague-Dawley rats were studied. Catheters were placed in the ventral tail artery and right jugular vein 24 hours before hemorrhage. Five experimental groups were created: sham (n=28), saline (n=62), NAL 1.0 mg/kg (n=63), NAL 5.0 mg/kg (n=22), and NAL 10.0 mg/kg (n=16). There were no significant differences between the experimental groups in body weight, % blood volume removed, MAP and MAP after hemorrhage. Each animal was bled quickly (3-4 ml/min) to a MAP of ~40 mm Hg and maintained at that pressure for 20 minutes at which time the treatment called for in the experimental design was administered. MAP was measured immediately after treatment and again at 10, 20 and 30 minutes. We found no evidence that NAL exerted any pressor effect. All treatments that required a saline bolus (saline or NAL) produced a significantly greater immediate rise in MAP than was seen with sham treatment ($p<0.001$). However, none of the NAL doses produced an effect different from saline. By 10 minutes after saline or NAL treatment, all animals including shams had achieved identical MAPs. All rats continued to spontaneously improve their MAP without any difference between groups for the remainder of the experiment. We conclude that NAL in saline has no pressor action different from normal saline in rats with hemorrhagic hypotension.

COMPARATIVE PHYSIOLOGY: RESPIRATION AND ACID-BASE

63.1

VENTILATORY RESPONSE TO NON-INSPIRED ENVIRONMENTAL CO_2 IN THE TEJU LIZARD. Gary O. Ballam. Lovelace Medical Foundation, Albuquerque, NM 87108

Adding CO_2 to inspired gas causes ventilatory depression in many lizards. It has been suggested that this response may be mediated by receptors located in the upper airways (UA) specifically, in the buccal, nasal or pharyngeal cavities (Comp. Biochem. Physiol., in press). In the present study the UA were isolated from inspired gases by blowing a gas mixture through the continuous arm of a "T" junction connected to an endotracheal tube. Elevating the CO_2 concentration to 1 to 4% in the UA while blowing fresh air past the endotracheal tube decreased ventilation 30 to 50% and lengthened the ventilatory pause between active efforts 100 to 375%. Mean inspiratory and expiratory flows changed -5 to -20%, inspiratory duration 26 to -8% and expiratory duration 0 to 30%. Tidal volume was unaffected. Adding 1 to 4% CO_2 in the inspired gas stream with fresh air in the UA caused ventilation to increase 9 to 45%. The ventilatory pause changed 13 to 480%, mean inspiratory and expiratory flows 12 to 100%, tidal volume 15 to 118% with variable changes in inspiratory and expiratory durations. Data from this study demonstrate the presence of a significant ventilatory reflex to low levels of CO_2 in the UA and imply the existence of CO_2 sensitive receptors in the UA. Supported by NIH grant #HL29342.

63.2

BLOOD OXYGEN ALTERS PREFERRED BODY TEMPERATURE IN LIZARDS. J.W. Hicks*, R.K. Dupre* and S.C. Wood. Dept. Physiology, University of New Mexico, School of Medicine, Albuquerque, NM 87131.

Exposure to external hypoxia (lowered lung PO2) evokes a variety of physiological adjustments which improve oxygen conductance. An option uniquely available to ectotherms is the behavioral reduction of body temperature (Hicks and Wood, The Physiologist, 26:A-49). The decrease in body temperature may represent a generalized response to impaired oxygen transport. To test this hypothesis, we established a temperature gradient and determined the preferred body temperature for Iguana iguana, Ctenosaura pectinata and Varanus exanthematicus. Body temperature was measured during external hypoxia (FIO2= 0.075) and before and after a 50% reduction in blood O2 capacity while breathing room air. The O2 capacity was reduced by blood volume replacement with the animals plasma. Arterial blood gases were measured throughout the experiments. The response of all three species was similar to that previously reported: a behavioral reduction in the preferred body temperature. The reduction in body temperature is independent of PaO2 or PaCO2 and appears to occur at a critical arterial O2 content. This study indicates that lizards subjected to hypoxic stress (whether external or internal) reduce their demands for oxygen by behaviorally lowering their preferred body temperature. Research supported by NSF Grant PCM-8300472.

63.3

IN VITRO AND IN VIVO PROPERTIES OF BLOOD IN THE TEGU LIZARD: EFFECTS OF TEMPERATURE AND CO2. S.C.Wood, M.L. Glass*, N. Heisler, and N. Andersen*. Abteilung Physiologie, Max-Planck Inst. Expt. Med., D-3400 Goettingen, FRG.

The respiratory properties of blood and in vivo blood gases and pH were investigated in 19 Tupinambis negropunctatus, ca. 1 kg mass) as a function of body temperature (25 or 35 C) and hypercapnia (7% CO2 breathing at 25 C). The "constant relative alkalinity" hypothesis and the two-compartment shunt model were tested. From 25 to 35 C, pHa decreased from 7.586 to 7.498; i.e., dpH/dT = -0.09, half that required for maintenance of a constant OH/H. The tegu, unlike species conforming to constant OH/H, increases ventilation with body temperature. Arterial PCO2 increased but only from 20.6 to 24.5 torr. With heating P50 increased from 42.3 to 49.6 @pH 7.4 and from 34.9 to 46.8 at in vivo pH values. Temperature sensitivity was about 1/4 that of mammalian blood (dH = - 3.1 kcal/mol). During breathing of 7% CO2/21% O2, arterial pH fell to 7.28 as PaCO2 increased to 49 torr. Arterial saturation decreased from 89 to 82% during heating but remained constant during CO2 breathing. As predicted by the two-compartment model, arterial PO2 increased from 61 to 71 torr during heating, despite the drop in saturation. With CO2 breathing at 25 C the P50 increased to 47.3 torr. but with saturation constant, PaO2 increased from 61 to 85 torr. Research Supported by Max-Planck Institute and NSF Grant PCM-8300472.

63.4

VENTILATORY RESPONSES OF THE MEXICAN BLACK IGUANA TO HYPOXIA AND HYPERCAPNIA AT DIFFERENT TEMPERATURES. R.K.Dupre*,J.W.Hicks* and S.C.Wood. Univ. New Mexico, Albuquerque,NM 87131.

The ventilatory responses and blood gases of the Mexican black iguana (Ctenosaura pectinata) were examined during graded hypoxia at different temperatures. Black iguanas increased pulmonary ventilation in response to hypoxia by increasing both respiratory frequency and tidal volume. The fractional inspired O2 concentration at which ventilation began to increase varied with temperature. The ventilatory threshold increased from ca. 5% O2 at 25C to ca. 7% O2 at 30C to ca. 9% O2 at 35C. A "gasping" pattern was also noted, the frequency of which increased with progressive hypoxia and increasing temperature. Breathing 3% CO2 resulted in an increased pulmonary ventilation above control by increases in both respiratory frequency and tidal volume. At 35C, 3% CO2 breathing also shifted the fractional O2 concentration at which the ventilatory response to hypoxia began to ca. 12% O2. The PaO2 at the hypoxic threshold increased with an elevation of body temperature. Our results agree with those of Glass et al. (J. Comp. Physiol. 151:145) and suggest that the respiratory control system of reptiles may cue on arterial saturation or arterial oxygen content rather than PaO2 for the modulation of pulmonary ventilation. Research supported by NSF Grant PCM-8300472.

63.5

VENTILATORY AND ACID-BASE RESPONSES TO LONG TERM HYPERCAPNIA IN FRESHWATER TURTLES. Randi B. Silver* and Donald C. Jackson. Div. Biol. & Med., Brown Univ., Providence, RI 02912.

The response to hypercapnia was studied in western painted turtles, Chrysemys picta bellii at 20°C. Ventilation, metabolic rate, arterial blood gases, and blood pH were monitored periodically on individual turtles exposed to 6% CO_2 for 72 hours. Plasma was analyzed for ions (Na^+, K^+, Cl^-, total Ca, total Mg). Ventilation increased 10-15 fold in the 1st hour of hypercapnia and was maintained for the entire exposure. The first hour of CO_2 breathing caused an increase in $PaCO_2$ from 24 to 39 mm Hg with a concomitant decrease in pH and rise in HCO_3^-. A further elevation in HCO_3^- from 42 to 50 mM/L was reached by the 24th hour of CO_2 breathing and was maintained for the remainder of the hypercapnic period. Small, significant increases in total Ca and Mg were found; however, no changes were observed in plasma [Na^+], [K^+], or [Cl^-], and the overall change in measured strong ions could not account for the increased [HCO_3^-]. Maximum HCO_3^- levels attained in Chrysemys exposed to more severe acidosis (14% CO_2) for up to 18 hours were the same as 6% CO_2 (10 mM), suggesting that an upper limit exists for the accumulation of [HCO_3^-] at 20°C. Upon recovery in air pH and [HCO_3^-] returned to control values within 5 hours. [HCO_3^-] was restored more slowly and was still elevated after 48 hours.
Supported by NSF Grant PCM82-02419.

63.6

ACID-BASE AND IONIC RESPONSES TO PROLONGED ANOXIA AT 10°C IN FOUR SPECIES OF FRESHWATER TURTLES. Donald C. Jackson and Gordon R. Ultsch*. Brown Univ., Providence, RI 02912 and Univ. of Alabama, Tuscaloosa, AL 35486.

Plasma ionic and acid-base variables were measured during anoxic submergence at 10°C on Chrysemys picta, Chelydra serpentina, Sternotherus odoratus, and Trionyx spiniferus. All turtles developed combined respiratory and metabolic acidosis, but the relative importance of the two forms of acidosis and the rate of development of blood acidosis differed significantly. The turtles with the most effective extrapulmonary gas exchange, Sternotherus and Trionyx, had the mildest respiratory acidosis; however, the rate of accumulation of plasma lactate was highest in these same species, so that severe acidosis (pH = 7.0-7.2) was reached earlier (3 days and 2 days, respectively) than in Chrysemys and Chelydra (10 days and 4 days, respectively). A similar pattern of compensatory strong ion changes, (elevated total Ca, total Mg, and K^+, and reduced Cl^-) occurred in each species. The effectiveness of these changes in balancing the elevated lactate was markedly different, however, ranging from 60% in Chrysemys and Sternotherus to 47% in Chelydra and 34% in Trionyx. We conclude that the ability of turtles to survive prolonged anoxia is related to the acid-base consequences, and that compensatory ion exchanges and reduced anaerobic lactate production rate are primary adaptive mechanisms.
Supported by NSF grant PCM82-02419 and the Research Grants Council of the Univ. of Alabama.

63.7

OXYGEN DIFFUSING CAPACITY IN ANESTHETIZED DUCKS DURING REST AND HYPERMETABOLISM. **S.C. Hempleman* and F.L. Powell. Dept. of Medicine, Univ. of California, San Diego 92093.**
Measurements of DO_2 in resting ducks suggest that arterial oxygenation can be severely impaired unless oxygen diffusing capacity increases with increasing metabolic rate. Since many birds tolerate heavy levels of exercise, some at high altitude, we decided to measure the change in DO_2 occuring with 2,4-dinitrophenol(DNP)-induced hypermetabolism. Pulmonary O_2 and CO_2 exchange was measured in three ducks being continuously unidirectionally ventilated with a hypoxic gas mixture. The ducks tolerated 5 mg/kg DNP well, resulting in increases in $\dot{M}O_2$ of 1.45, 2.41, and 1.31 fold. DO_2 increased in almost direct proportion (1.29, 2.43, and 1.25 fold, respectively). One other duck given normoxic inspired mixtures tolerated 15 mg/kg DNP and increased $\dot{M}O_2$ 4.5 fold, but we found that DO_2 values measured in normoxia underestimated hypoxic values, apparently due to the nonlinear O_2 dissociation curve in normoxia. The mechanisms for increase in DO_2 with increasing metabolic rate remain unclear, but may include changes in pulmonary capillary recruitment, blood volume, or decreases in functional lung inhomogeneity. **NIH ROl HL26050 and 5T32 HL07212.**

63.8

BOHR EFFECTS AND RED CELL ORGANIC PHOSPHATES IN WHOLE BLOOD OF ADULT HOUSE SPARROW. Leigh A. Maginniss and Joanna Rumerman*. Div. of Biology & Medicine, Brown Univ., Providence, RI 02912

CO_2 and fixed acid Bohr effects ($\Delta \log P_{O2}/\Delta pH$) were determined for Passer domesticus at 35, 41 and 45°C using a thin blood film technique. At each temperature, the CO_2 Bohr slopes were similar at P_{50} (35°, -.48; 41°, -.49; 45°, -.49). The CO_2 coefficients were also reasonably saturation independent between 10 and 90% S. Fixed acid Bohr effects were significantly less than the corresponding CO_2 slopes at P_{50} (35°, -.43; 41°, -.39; 45°, -.41). The difference between CO_2 and H^+ Bohr effects, assumed to represent carbamino CO_2 binding to Hb, decreased in magnitude with increasing saturation at each temperature. The formation of oxylabile Hb-carbamate in Passer, a condition not previously observed in fresh avian blood, may be due to the specific organic phosphates in sparrow RBC's. Inositol pentaphosphate (IPP, 3.1 µmol/ml RBC) and ATP (7.7 µmol/ml RBC) were the major organic phosphates in Passer red cells. The ratios of organic phosphate to Hb tetramer for IPP (.69) and ATP (1.71) in Passer were lower and higher, respectively, than reported for most other avian species. Since the IPP to Hb_4 ratio is substantially less than unity, ATP may also function as an important allosteric modifier. And if ATP exerts a reduced binding affinity for sparrow Hb as shown for other birds, CO_2 may compete more effectively in the formation of Hb-carbamate.
(Supported by NSF PCM 8202702).

63.9

PULMONARY DEVELOPMENT IN GROWING GUINEA PIGS EXPOSED TO CHRONIC HYPERCAPNIA. Andrew J.Lechner[1], Cynthea I. Blake*, and Natalio Banchero. Depts. Physiology, St.Louis Univ.[1] and Univ.Colorado Schools of Medicine, St. Louis, MO, and Denver, CO.

The role of increased lung stretch in accelerated lung growth was studied in young male guinea pigs (Hartley) which chronically hyperventilated due to high CO_2. Weanlings (BW= 268±11 g, X̄±SEM) breathed either room air (n=14) or 5.2% CO_2 in 21% O_2,balance N_2 (n=13) for 4 weeks at 22.5°C. At 3-4 weeks of exposure, ventilation, Ve= 41.9±2.7 ml/g/hr for controls and 89.6±6.9 ml/g/hr for experimentals (P<0.001), while V_{O_2}= 1.18± 0.06 and 1.27±0.06 ml/g/hr respectively (ns). Animals were anesthetized and their lungs either (a) excised, lyophilized to constant weight (W_L), and analyzed for total DNA and blood-free protein, or (b) fixed in situ (intratracheal 2% glutaraldehyde, Pt= 22 cmH_2O) for volume measurement (V_L) and morphometry with light and electron microscopy. In controls, final BW= 457±15g, V_L= 18.4±0.5ml, alveolar surface area, Sa=1.31±0.07m^2, membrane diffusing capacity, Dm= 5.52±0.50 ml O_2/min/mmHg, W_L= 0.77±0.06g, DNA= 13.4±1.7mg, and protein= 0.50±0.05g. For the hypercapnic group, BW= 474±15g, V_L= 16.8±0.9ml, Sa= 1.56±0.12m^2, Dm= 6.63±0.66 ml O_2/min/mmHg, W_L= 0.64±0.04g, DNA= 11.3±0.8mg, and protein= 0.41±0.02g. None of these differences were significant. Increasing lung stretch by hyperventilation did not stimulate pulmonary development, at least in normoxia and when V_{O_2} remained constant. (Supported by the American Lung Association and NIH grants HL-28849 and HL-29640.)

63.10

RESPIRATORY WAVES (RW) IN THE ARTERIAL BLOOD PRESSURE OF BIRDS. Clanton, T.L, R.P. Kaminski*, G.O. Ballam and A.L. Kunz. Department of Medicine and Physiology, The Ohio State University, Columbus, OH 43210.

In awake or decerebrate birds, oscillations in arterial blood pressure were observed to occur with the same period as breathing movements. RW ranged from 5 to 10 mm Hg (mean pressure), depending on the level of ventilation. The maximum pressure occurred during mid-expiration. The minimum occurred during mid-inspiration. RW were associated with some degree of sinus arrhythmia; heart rate increased during inspiration and decreased during expiration. When the birds were unidirectionally ventilated, changes in intrathoracic (air sac) pressure (± 0.2 cm H_2O) generated by breathing movements were nearly eliminated. Under these conditions RW were still present at a normal level of CO_2 drive. When the decerebrate birds were unidirectionally ventilated and paralyzed with succinyl choline, RW remained synchronized with respiratory motor nerve activity as measured from L_1. Following vagotomy, RW were augmented. Under all the above conditions the phase relationship between RW and breathing pattern remained unchanged. These results suggest that a large component of RW in birds is not associated with breathing movement and comes from non-vagal efferent nerve activity innervating the heart or vasculature that is modulated by respiratory center activity.
Supported by the Central Heart Chapter, AHA.

TEACHING MATERIALS AND METHODS

64.1

USE OF "SELECTIVE LABORATORIES" IN TEACHING CARDIOVASCULAR PHYSIOLOGY IN MEDICAL SCHOOL. John C. Conklin,* and David E. Cowen* (SPON: D.C. Randall). Dept. Physiol and Biophys., Univ. of Kentucky, Lexington, KY 40536.

Use of anesthetized dogs in a traditional medical school laboratory setting provides useful, but limited insight into the function and regulation of the cardiovascular system. The "selective laboratory" concept (Physiologist 25:343, 1982) has permitted exploration of similar phenomenon in awake dogs. An initial laboratory was performed as part of a physiology course; the response of a 20 kg pentobarbitol-anesthetized dog was described during bilateral carotid occlusion, vagal nerve stimulation, and sequential infusion of phenylephrine (200 µg), nitroglycerine (0.3 mg), and dobutamine (320 µg) before and after β-blockade (propanolol, 20 mg). Portions of this experiment were repeated in another dog surgically prepared with an indwelling aortic pressure catheter, a Konigsburg left ventricular pressure transducer, and ultrasound length crystals in the left ventricular myocardium. Following a 2 week recovery, the same drugs were administered in identical dosages and sequence. The value of the laboratory rested largely in the availability of specialized instrumentation and individualized instruction in the prosecution and interpretation of the experiment. The experiment enhanced understanding of the cardiovascular response mechanisms evoked in the unanesthetized animal and underlined the importance of research in contemporary medical physiology.

64.2

EXAMINATIONS BY COMPUTER. H. G. Hempling, Dept. of Physiology, Med. Univ. of S. Carolina, Charleston, S.C. 29425

These programs in BASIC for the APPLE II + or (E) are for the teacher with only a peripheral interest in computers and a central interest in good teaching.* The teacher does the following: a. Prepares a pool of questions. 100 questions per disc. These are usually multiple choice, but may include a word or number as an answer. b. Prepares an answer key. c. Prepares a class list.

The programs provide the following options in order of complexity. 1. A simple examination. Students are presented with a pool of questions and answer them in order. Answers are recorded and graded at teacher's convenience. 2. Teacher selects questions from multiple pools and merges them into a single exam. 3. Questions are selected at random from multiple pools of questions and merged into a single exam. 4. Student has access to multiple pools of questions. He requests an exam. Questions are selected at random. Student takes exam and receives a grade which is accessible to teacher. Student requests a review of incorrect answers. In response he receives a discussion of each incorrect answer. This latter option requires that the teacher prepare a text of explanations to parallel each question. This latter option converts the exam into a learning experience.
*Send a blank, 16 sector floppy disc and postage to cover return mail.

64.3

EXPERT SYSTEM USED AS A TEACHER OR CONSULTANT IN PROBLEMS OF HEMOSTASIS. G. Kaldor , E. Mammen*and R. Rada.* VAMC, Allen Park, MI 48101 and Departments of Pathology, Surgery and Computer Science, WSU, Detroit, MI 48201

A knowledge based computerized expert system suitable for both consultation and teaching the applied physiology of hemostasis was developed. The following major areas are included. 1. The clinical physiology of bleeding. 2. The effect of factor deficiencies and circulating anticoagulants on the hemostasis. 3. The pathophysiology of multiple abnormalities of the cascade, e.g. liver disease and D.I.C. The model requires platelet count and bleeding time as the minimal information to assess platelet involvement in a bleeding problem. Prothrombin time measures the extrinsic pathway, activated partial thromboplastin time evaluates the intrinsic pathway and thrombin time determines the fibrinogen-fibrin conversion and euglobulin lysis estimates the proteolysis (plasmin activity) of the blood. Repeated testing of mixtures of normal plasma plus patient plasma is used to distinguish between factor deficiencies and inhibitors. A fair number of other specific laboratory tests are also included if these tests are required to determine the precise nature of the coagulation defect. The program is flexible. Minimal interaction is needed with the user if it serves as a consultant. On the other hand as a teacher the model calls for a great deal of interaction with the user in the form of questions and answers. As a knowledge based expert system it can explain the physiological basis of every decision it makes.

64.4

ENHANCEMENT OF A COMPUTER MODEL FOR TEACHING RENAL PHYSIOLOGY. Fred R. Sias, Jr. and Richard J. Roman. Clemson University, Clemson, S.C. 29631 and The Medical College of Wisconsin, Milwaukee, WI 53226.

The increasing cost of animals and the difficulty of single-nephron experiments makes the computer a valuable addition to the teaching laboratory. It is particularly useful to be able to manipulate parameters that would be difficult to modify in an animal experiment, and to observe variables that are difficult or impossible to access in the laboratory. Many computer models have been developed that provide a detailed understanding of aspects of renal function; however, few models have attempted to simulate the entire kidney function as it interacts with the rest of the cardiovascular system. The model predicts urine flow, urine osmolarity, sodium excretion, etc. as a function of neural and hormonal inputs to the kidney, arterial pressure and the cortical-medullary osmotic gradient. It includes an interactive control section that allows the user to modify any of a list of parameters and observe the effect on variables such as urine output, concentrating ability, blood-flow autoregulation, glomerular-tubular balance, etc. We have provided a spread-sheet type presentation that allows the user to modify selected parameters and observe the effect on a set of variables. Each parameter change adds another line to the display that includes the modified parameter and the effect on the output variables. A preliminary workbook including a number of suggested exercises directs the student in the use of the model. (NIH grants AG01794 and P01 HL29587)

64.5

EXCITATION AND CONDUCTION PROPERTIES OF MEMBRANES AS ILLUSTRATED EXHIBITED BY THE COMPOUND ACTION POTENTIALS OF FROG NERVE. Fred E. Williams, Baylor College of Dentistry, Dallas, TX. 75246.

An understanding of excitable membrane properties and particularly action potentials is necessary in health care students who will interpret and treat sensory and motor abnormalities. This tape reviews and illustrates the excitation properties and conduction characteristics of excitable membranes for those previously introduced to the resting membrane potential and action potentials. The topics discussed include: 1.) action potentials verses compound action potentials, 2.) electrical stimulus variables, 3.) threshold stimuli and membrane excitability, 4.) summation of subthreshold stimuli, 5.) refractory periods, 6.) multiple peaks of compound action potentials, 7.) speed of action potential conduction, 8.) alteration in conduction by local anesthetics, 9.) alterations produced by hyperkalemia, and 10.) alterations produced by hypocalcemia.

AUTHOR INDEX

Anaerobic Threshold

Presented at the Meeting
of the
American Physiological Society

Lexington, Kentucky
August 27, 1984

1984 Refresher Course
Syllabus

Edited by
Daniel R. Richardson and L. Bruce Gladden

ANAEROBIC THRESHOLD

A Refreser Course

Presented at the Meeting
of the
American Physiological Society
Lexington, Kentucky
August 27, 1984

Organized and Edited by
Daniel R. Richardson and L. Bruce Gladden

Course Outline

Historical Development of the Anaerobic Threshold Concept

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University of Louisville, School of Medicine
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Introduction

Prehistoric man presumably associated running from predators or danger with an increase in breathing effort, but an understanding of the mechanisms of this response has necessitated much in the way of original scientific investigation (Figure 1). The relationship between the act of respiration and life processes has, no doubt, also been long recognized and the ancient philosopher/physicians drew upon this relationship in consideration of the soul and spirits of the body.

Pivotal Papers in the Development of the Anaerobic Threshold Concept

1907 Fletcher and Hopkins ↑LA in living tissue

1914 Christiansen, Douglas and Haldane
CO_2 from LA buffering by HCO_3^-

1930 Owles LA threshold in man

1964 Naimark, Wasserman and McIlroy
↑R beyond LA threshold

1964 Wasserman and McIlroy
Definition of the concept

Figure 1.

Galen of Pergamon (ca. 130-201 A.D.) followed the ideas of Hippocrates, Plato and Aristotle in the development of an anatomical/physiological system of thought. Among other accomplishments (such as some 400 written manuscripts) he was the physician for the Roman gladiators and, later, personal physician for the Roman Emperor, Marcus Aurelius (15). Galen was the first experimentalist, but he maintained his philosophical ties to his predecessors, particularly with reference to the concepts of pneuma and the soul. He reasoned that the function of respiration was to provide the body with air which was necessary to sustain life processes. Galen, in his magnificent work "On the Usefulness of the Parts of the Body" states (8): "If, then, life is an action of the soul and seems to be greatly aided by respiration, how long are we likely to be ignorant of the way in which respiration is useful? As long, I think, as we are ignorant of the substances of the soul" (6).

What of the substances of the soul that influence respiration and make it "useful"? The Galenic system of physiology dominated scientific thought for the next thousand years, but the question posed above was not really addressed until the discoveries and writings of the great French scientist (educated in Law) Antoine-Laurent Lavoisier (1743-1794) struck down the phlogiston theory and altered the theoretical concepts of chemistry (15). Lavoisier demonstrated that respiration consumed oxygen (which he named) and produced carbon dioxide. While he apparently thought this metabolic process occurred in the lungs rather than in the peripheral tissues, he did show in 1793, while working with Armand Séguin that the oxygen consumption ($\dot{V}O_2$) was slightly greater than the carbon dioxide production ($\dot{V}CO_2$) (8, 14). Séguin and Lavoisier (17) reasoned that this indicated some of the oxygen was used to combine with hydrogen to form water. They further showed that exercise increased this oxidation.

By the end of the 18th century, the concepts of chemical oxidation and respiratory physiology were linked and it was clear that oxygen was required for life processes and that carbon dioxide and water were the products of this activity. The link between metabolic activity, alterations in the ratios of $\dot{V}O_2$ and $\dot{V}CO_2$, and the role of hydrogen from fixed acids was still more than a hundred years away.

Lactic Acid Formation During Exercise

It was not until the first few decades of the 19th Century that the application of quantitative chemistry and physics to physiological questions finally brushed aside the strong vitalist concepts of the past. Questions concerning metabolism were among the first in physiology to be investigated through chemical analysis (15). In the early part of the 19th Century many investigators began efforts to discover the composition of animal structures. It became clear that carbon dioxide and lactic acid were formed as a result of the activity of the cells. The leaders in this development of chemistry as a tool in physiological investigations (perhaps appropriately described as biochemistry) included Justus von Liebig (1803-1895) and Felix Hoppe-Seyler (1825-1895). The other front in the attack on vitalism was pursued by Carl Ludwig (1816-1895) and Emil H. DuBois-Reymond (1818-1896), among others, who emphasized physical laws in physiological research (perhaps the beginnings of biophysics).

Du Bois-Reymond, in 1860, was one of the first investigators to recognize and measure lactic acid formation within skeletal muscle (15). Others noted that lactic acid formation in muscle was associated with contractions and

indicated the advance of fatigue (10). Trasaburo Araki, in 1891, while working in Hoppe-Seyler's laboratory in Strassburg, described hypoxia-induced lactic acid formation (1).

In the early 1900's, Walter Morley Fletcher (1873-1933) began his investigations into the metabolism of skeletal muscle. Fletcher was educated at Cambridge and studied medicine at St. Bartholomew's Hospital. He returned to Cambridge and as a Senior Demonstrator in the Physiology Laboratory had as a pupil a young man by the name of Archibald V. Hill (5). Fletcher was a physiologist and apparently somewhat of an athlete, thus his interest in the metabolism of muscle. In 1907, Fletcher published a classic paper in the history of the anaerobic threshold entitled, "Lactic Acid In Amphibian Muscle" (4). This work was done in collaboration with Frederick Gowland Hopkins (1861-1947), who was educated at University College and Guy's Hospital and was the founder of biochemistry in Britain (5, 15). In this very careful and meticulous investigation, Fletcher and Hopkins demonstrated that 1) resting muscle contained very little lactic acid, 2) mechanical injury or irritation could increse the lactic acid concentration, 3) lactic acid can be produced by viable muscle under anaerobic conditions, 4) fatigue due to contraction of the muscle was associated with an increase in lactic acid and 5) hyperoxia depressed lactic acid formation. The work of Fletcher and Hopkins, who were later knighted, was the beginning of the clarification of lactic acid's role in exercise metabolism. Their careful analyses demonstrated for the first time that previous measures of lactic acid in minced resting muscle were inaccurate due to lactic acid release from injury during surgical removal and mincing and due to extractions in water or room temperature alcohol rather than chilled alcohol. Their analyses clearly demonstrated that lactic acid was a metabolic product of living tissue, an observation which provided the necessary background for subsequent investigations leading to the development of the anaerobic threshold concept.

In 1909, J. H. Ryffel (16), in the Proceedings of the Physiological Society, showed in man that "violent muscular exercise" produces a considerable increase in blood lactic acid. Johanne Christiansen, Claude Gordon Douglas and John Scott Haldane (2) followed up on the report by Ryffel and proved that in severe muscular work the lactic acid and bicarbonate combine to form CO_2 and that this additional CO_2 (additional to the CO_2 produced by the increased metabolic activity) must also be "expelled" by respiration (Figure 2). The bicarbonate concentration in the blood is diminished and the lactic acid in the blood would stimulate the respiratory center so that alveolar CO_2 pressure would also be reduced below the resting value, the end result being a decrease in the CO_2 combining power. This represents one of the first descriptions of the gas exchange consequences of severe exercise and lactic acid formation in the muscles. Douglas provides an excellent review and the first description of the anaerobic threshold in a paper presented in the Oliver-Sharpey Lecture series published in The Lancet in 1927 (3). This brief paper is highly recommended for the interested reader.

The first account of the blood lactic acid changes that occur for a range of exercise intensities was published in 1930 by Douglas' student, W. Harding Owles (13). This very carefully controlled study provides much data collected from the two subjects, Owles and Douglas. The results of this study were 1) there exists on the basis of two subjects) a critical metabolic level below which blood lactic acid does not increase and above which it does increase, 2) this critical exercise level varies between subjects and types of exercise (treadmill vs bicycle) and, 3) the CO_2-combining power of the blood is reduced at intensities above this critical level but not below it. Thus Owles, in 1930, described the anaerobic threshold from the blood lactic acid alterations due to exercise. These blood lactate changes over a range of intensities of exercise were subsequently substantiated by Rodolfo Margaria, H. T. Edwards and David Bruce Dill in 1933 (11). These authors demonstrated that, in human subjects performing treadmill exercise, no additional lactic acid appears in the blood until a work rate of approximately two-thirds of maximum is reached, after which lactic acid increases rapidly. By this time the blood lactate changes during exercise were clearly established and further exploration in this area involved, for example, altering inspired oxygen tension and blood oxygen delivery to metabolically active tissue (9). With the advent of rapidly responding gas analyzers it became possible to critically address the gas exchange consequences of blood lactic acid changes during exercise.

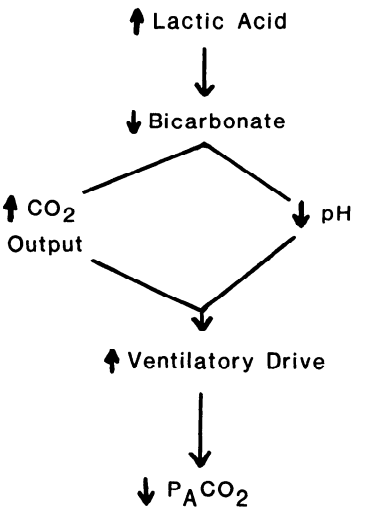

Figure 2. Schematic of the consequences of lactic acid formation

Anaerobic Threshold and Gas Exchange

From the work of Douglas and others, it can be concluded that the release of CO_2 from bicarbonate during lactic acid buffering (Figure 2) is responsible for an increase in the gas exchange ratio (R). Naimark, Wasserman, and McIlroy, in 1964 (12), used this observation to investigate the continuous measurement of R during exercise as an index of cardiopulmonary functioning in the balance between oxygen supply and demand in working muscles. They obtained breath-by-breath measurements of R and periodic arterial blood samples in normal subjects and patients (mitral stenosis or pulmonary hypertension) over a range of bicycle ergometer work rates. The observed lactic acid changes were similar to those described by Owles but they also reported a

range of exercise intensitites below which bicarbonate in the arterial blood, and R, did not appreciably change. These observations are consistent with the concept of bicarbonate buffering of lactic acid and the resultant increased or "excess" CO_2. Figure 3 is a schematic representation of the relationship between R and metabolism during exercise, as described by these authors (their Figure 10). This particular Figure from their paper has become pivotal in subsequent discussions of the anaerobic threshold.

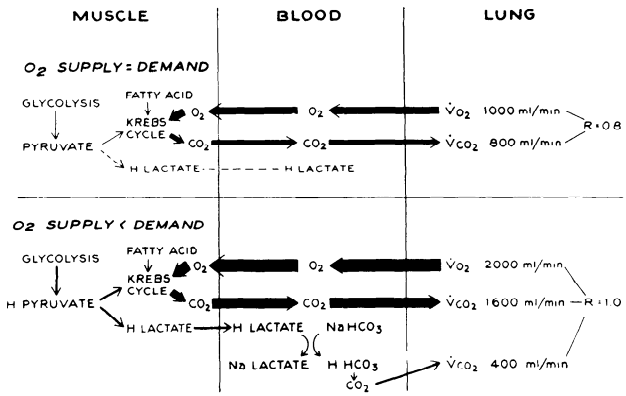

Figure 3. Schematic of the relationship between R and metabolism (From Ref. 12, pg. 650, figure 10.)

Later in 1964, Wasserman and McIlroy (18) presented the first definition of the "anaerobic threshold" in a paper using the same techniques of breath-by-breath R determination and arterial blood sampling during incremental exercise of cardiac patients. Figure 4 is important in their definition, which follows:

> "When R, during the last 30 seconds of each workload, is plotted against oxygen consumption, a sigmoid curve is usually obtained (Figure 4). The steepest part of this curve indicates the level of oxygen consumption at which anaerobic metabolism becomes important, and we call this the 'threshold' of anaerobic metabolism. It corresponds to the point at which the concentration of bicarbonate in the arterial blood decreases and the concentration of lactate rises. (References to 12 and 7)."

This definition was, some time later (19), slightly altered to describe "the level of work or O_2 consumption just below that at which metabolic acidosis and the associated changes in gas exchange occur."

I have not addressed all of the published work in this area nor have I included the mnay works challenging this concept; the subsequent papers in this refresher course will address the many implications of this concept. It has been this author's intent to provide a base for the subsequent papers and to enlighten the consideration of how the substances of the soul and respiration are useful. So to conclude, I offer the remainder of Galen's thoughts on these matters. "But we must nevertheless be daring and must reach after Truth, and even if we do not succeed in finding her, we shall at least come closer than we are at present" (6).

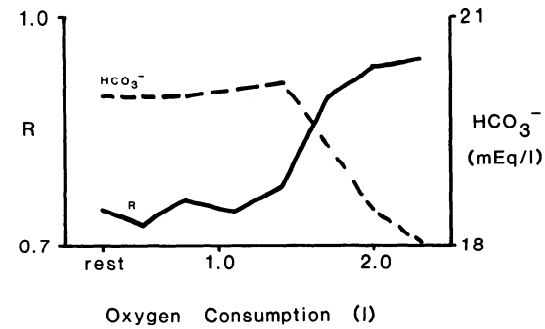

Figure 4. Changes in R and HCO_3^- during graded exercise (Redrawn from Ref. 18, pg.847, figure 3.)

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Mechanisms of Blood Lactate Increase During Exercise

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Introduction

Lactate metabolism during physical activity has been reviewed by numerous researchers (e.g. 2, 6, 7, 19) and these can be consulted for a more complete understanding of the entire area. This paper will review only those components that directly apply to the initial accumulation of blood lactate above resting levels during progressive exercise. This is the blood lactate aspect of the concept termed 'anaerobic threshold'. However, this concept also includes changes in both blood gases and pulmonary responses. Thus, in this paper the initial increase in blood lactate will be termed "Owles' point" (19) out of respect to the work of Owles in 1930 (34). Owles' point normally occurs at power outputs requiring approximately 50-70% of $\dot{V}O_2$max. This presentation will review the changes in intramuscular lactate production and concentration, muscle to blood lactate exchange and blood lactate clearance that result in the increase in blood lactate at these work intensities.

The Form of Lactate

While the terms 'lactic acid' and 'lactate' are often used as synonyms, one should bear in mind that the former is an undissociated acid and the latter is a freely dissociated ion. The pK of lactic acid is 3.86 and thus, in a physiological solution, the ionic form represents virtually all of the substance. Researchers measure lactate in blood samples and muscle biopsies, but lactic acid may be a major form as the molecule crosses cell membranes (32). Furthermore, lactate exists as L(+) and D(-) isomers; and in routine lactate measurements, the assay is specific for L(+) lactate. The D(-) or dextro form does have metabolic significance as the end product in the aminoacetone pathway in which threonine and glycine are metabolized to D(-) lactate (10); human skeletal muscle appears to employ this pathway and blood levels of the D(-) form in exercising man increase by 70% (10). However, since L(+) lactate increases approximately 800% in the same situation, it will be assumed to be the important component and the term 'lactate' will imply the L(+) isomer.

The Blood Lactate Response

Workers in the 1920's and 1930's (1, 12, 34) demonstrated that blood lactate increases exponentially with increasing exercise intensity. As exercise intensity increases, blood lactate remains constant or even declines during light work ($<$50% $\dot{V}O_2$max). At work loads demanding 50-70% $\dot{V}O_2$max blood lactate begins to increase; the exact exercise intensity for Owles' point can vary due to the relative baseline chosen for increased lactate (e.g. above resting lactate level; $>$2mM; $>$4mM), the testing protocol (e.g. duration of workload, magnitude of each work increment and blood sampling site (arterial, arterialized venous, or finger tip)); and the physiological state of the subject (e.g. trained or untrained, fasted or carbohydrate-loaded).

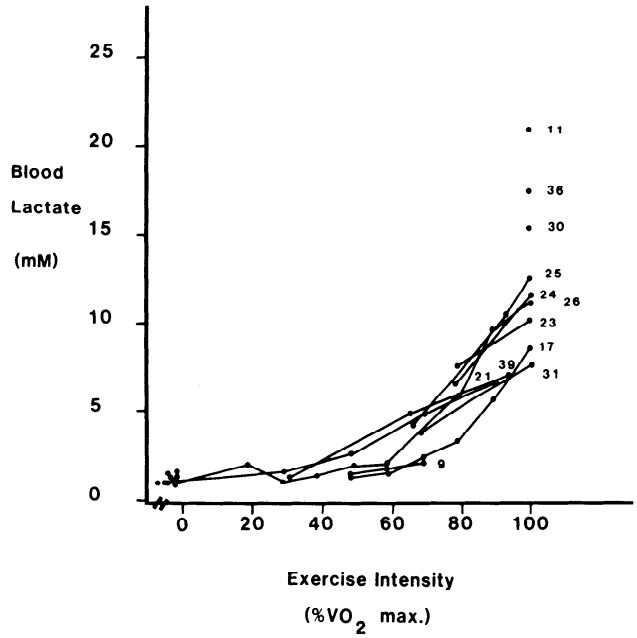
In order to gain an objective impression of the blood lactate response, the data from several studies (N=13) were averaged. All studies had similar progressive work task protocols and both blood and muscle lactate values were reported. The blood lactate data are presented in Figure 1. There is qualitative and quantitative variability between studies (see upper panel); however, if one analyzes the means of these investigations, a significant exponential relationship ($y = 0.82\ e^{2.30x}$; $r = 0.89$) is found between blood lactate and exercise intensity (Figure 1, lower panel).

Initially the increase in blood lactate was interpreted as the result of anaerobic glycoysis becoming involved in sustaining ATP supply (41). However, studies have demonstrated that the Owles' point can be altered by many factors that are independent of oxygen delivery and consumption. Thus several recent reviews (6, 7, 19) come to the conclusion that the phenomenon is complex and involves a hierarchy of metabolic modulation with the net result that more lactate is being released into the bloodstream (primarily from active muscle) than is simultaneously being cleared (by active and resting muscle, liver, kidney, etc.). Thus, the only 'threshold' aspect of the blood lactate response is that it is the first measurable evidence that an imbalance between lactate release and clearance has occurred as opposed to reflecting the sudden turning on of an accessory energy supply system. While the release/clearance balance is the determining factor, a fundamental underlying process is lactate production.

Lactate Production

In interpreting the lactate level in any tissue, it is important to appreciate that lactate production is virtually always present and forms a useful metabolic function. It is not a process that is only evoked due to tissue hypoxia. Within the enzymatic steps of glycolysis, glyceraldehyde 3-phosphate dehydrogenase produces glyceraldehyde 1,3-diphosphate and simultaneously reduces NAD^+ to NADH. The NAD^+/NADH cytoplasmic pool is quite small and without rapid recycling glycolysis would be limited by the rate of this reaction

(see Figure 2). It has been suggested (27, 33) that this step can limit the maximal glycolytic flux. The regeneration of the critical NAD^+ can be accomplished by the alpha glycerol phosphate and malate shuttle systems or by converting pyruvate to lactate via lactate dehydrogenase (LDH). Cohen and Woods (2) suggest that high levels of intramuscular lactate may limit performance by inhibiting this critical NAD^+ recycling function. This effect is independent of any H^+ effects.



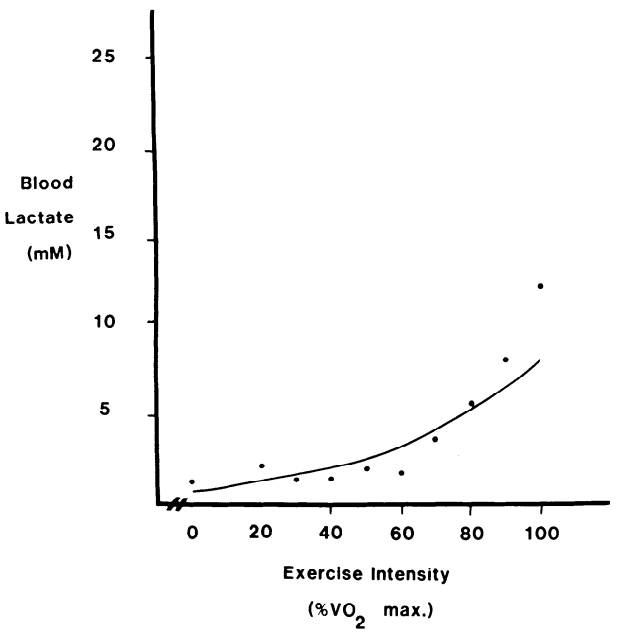


Figure 1. The blood lactate response to increasing exercise intensity. The data of 13 studies (identified by the reference numbers in the upper panel) were analyzed to demonstrate the 'typical' response and its variability. For consistency the work loads were expressed as a percentage of the $\dot{V}O_2max$. All available data from these studies for a given exercise intensity were averaged in the lower panel. The standard errors were very small and so were deleted. The line in the lower panel represents the exponential equation referred to in the text.

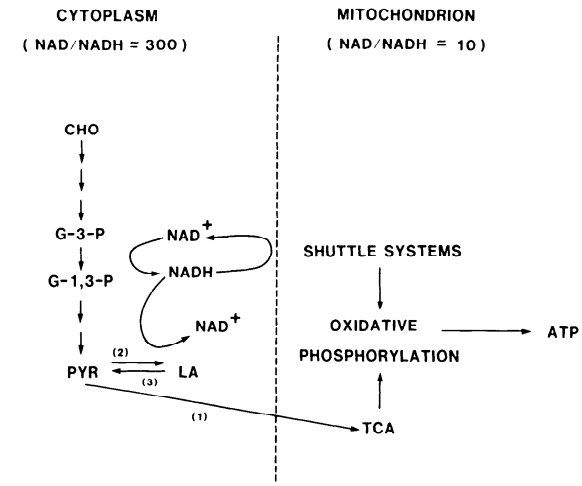


Figure 2. A schematic illustration of the role of the shuttle systems in maintaining the cytoplasmic redox state. The vertical line represents the mitochondrial membranes. Carbohydrate (CHO) is shown entering glycolysis and at one step glyceraldehyde 3-phosphate (G3P) is converted to glyceraldehyde 1,3-diphosphate (G1,3P) and NAD^+ goes to NADH. Either the shuttle systems or lactate (La) production (reaction (2)) recycle NAD^+. The glycolytic product, pyruvate (Pyr), has two major metabolic fates; lactate production and decarboxylation reaction (1) in the TCA cycle. The net lactate formed is the balance between the reduction and oxidation reactions (2 and 3).

Pyruvate and NADH are produced in equimolar quantities and are equal to the glycolytic rate. For lactate production, LDH uses a portion of these substances as substrates, but usually a large portion of the pyruvate is decarboxylated in the TCA cycle with a corresponding quantity of NADH being recycled via the shuttle systems. Thus, lactate production, while essential is usually far less than the glycolytic (pyruvate production) rate.

LDH exists in five isozyme forms which are all found in varying proportions in skeletal muscle. Those isozymes which favour pyruvate reduction to lactate (e.g. LDH-M form or LDH_1) predominate in the type II (fast twitch-glycolytic) fibers and those that promote lactate oxidation to pyruvate (e.g. LDH-H form or LDH_5) are higher in concentration in the type I (slow twitch-oxidative) fibers (37). These fiber types have complements of glycolytic and oxidative capacities such that type II fibers tend to be lactate producers and type I fibers tend to be lactate consumers. Since human skeletal muscle is a mosaic of type I and II fibers, a portion of the muscle may consume lactate while another portion of the muscle may be producing lactate. Lactate produced by type II fibers may actually diffuse across the interstitial space and into type I fibers, where it is oxidized to CO_2 and H_2O. In addition, studies employing labelled lactate in humans have demonstrated that skeletal muscle can be taking up lactate from the blood and oxidizing it even though there may be a net efflux occurring (14, 20). This occurred in both resting and

active muscle. During activity the rate of oxidation increased considerably both below and above Owles' point.

Factors influencing Net Lactate Production

The fiber type complement of a muscle, a genetically determined characteristic (29), and the morphological and enzymatic features associated with these fiber types have been shown to have significant correlations with the exercise intensity at which either Owles' point or the accumulation of blood lactate to 4mM occurs (16, 28, 38, 40). Characteristics such as high percentage of type I fibers, high capillary density and oxidative capacity, and low levels of glycolytic enzymes are associated with a delayed onset of accumulation of blood lactate.

Inheritance through fiber type characteristics gives skeletal muscle a basic potential for lactate production and oxidation, and ontogenetic factors such as one's state of training can further modify this predisposition. Inactivity or detraining lowers Owles' point, while endurance training elevates it (3, 36, 37). Sjödin (37) reported that endurance training decreased the total LDH and there was a relative increase in the LDH-H isozyme. Donovan and Brooks (4) concluded that endurance trained animals had lower blood lactate levels during exercise due to increased clearance of lactate while production rates were unaltered. In apparent contrast, Houston et al. (13) found that total LDH decreased with detraining and was not increased during a short retraining period. However, maximal blood lactate levels followed a similar pattern. Thus it appears that the quantity and quality of LDH can influence lactate production and/or clearance and these characteristics may be altered by activity patterns.

Superimposed on these enzymatic components are other factors in intracellular modulation of lactate metabolism. Substrate availability (especially glycogen (15)), enzyme modulators such as Ca^{2+}, ATP/ADP, NAD^+/NADH, Citrate, and H^+, as well as the direct or indirect effects of hormones such as insulin and the catecholamines alter both the glycolytic and lactate production rates. Factors known to influence blood lactate levels such as pedal speed (15, 31), oxygen availability (42), and acid-base status (7, 19) presumably act through the interactions of either hormonal or enzymatic modulators to alter the lactate production/oxidation balance and thus the Owles' point.

Lactate Release

It is frequently assumed that muscle lactate diffuses freely into the blood and subsequently that blood lactate reflects muscle lactate. However, in 1937 Sacks and Sacks (35) demonstrated that muscle lactate accumulated to four times the plasma level during activity. The muscle lactate data from those studies summarized in Figure 1 are presented for individual experiments in the upper panel of Figure 3 and summarized in the lower panel. Muscle lactate remains at resting level until approximately 50% $\dot{V}O_2$max at which point it begins an exponential rise ($y = 0.56\ e^{3.4x}$; $r = 0.91$). While qualitatively the response resembles that of blood lactate, the slope of the line is much steeper. The muscle to blood concentration difference widens to the extent that most studies report muscle lactate levels 1.5 - 2.5 times greater than the blood concentration, suggesting that lactate release ($\dot{L}a$) is not entirely a passive process.

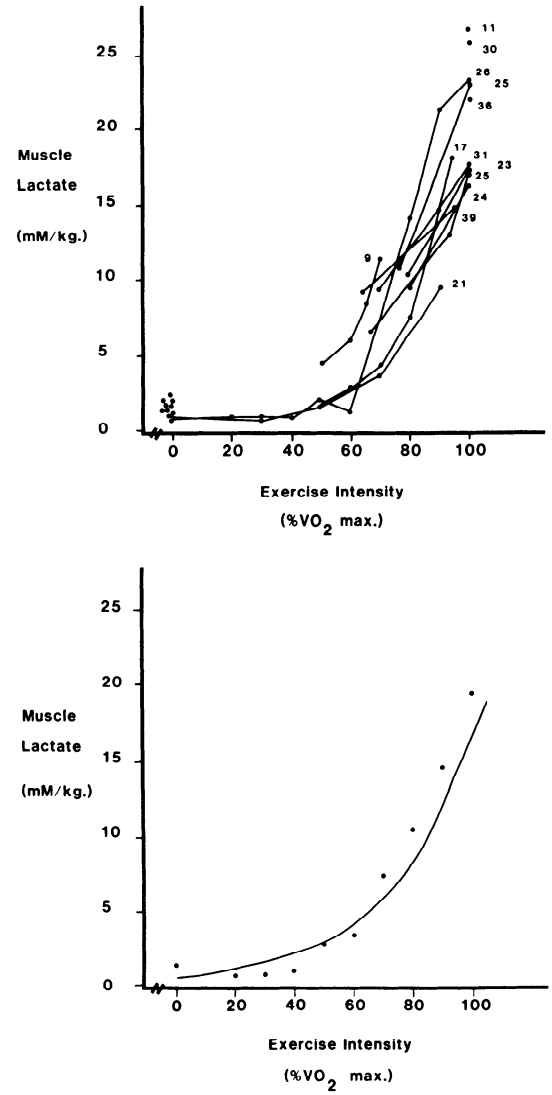


Figure 3. The muscle lactate response to increasing exercise intensity. The Figure is organized in the same manner as Figure 1 and the data are taken from the same studies.

Jorfeldt et al. (21) reported that $\dot{L}a$ increased linearly with muscle lactate concentration, but it reached a maximum of approximately 4.5 mM/min at an exercise intensity of 70% $\dot{V}O_2$max when muscle lactate concentration was only 4 mM/kg. They concluded that there was saturation of a translocation mechanism. While this concept may be correct, it should be noted that the study was limited in sample size (N=4) and only one of the four samples was obtained above the proposed saturation point. Researchers using a variety of tissue preparations have concluded that lactate exchange is not passive and that it involves facilitated or active transport mechanisms (e.g. 2,5,7). Furthermore, Mainwood and Worsley-Brown (32) demonstrated that changes in external H^+ concentration of skeletal muscle dramatically altered both $\dot{L}a$ and the relative quantities of lactate crossing the membrane as the ion and the undissociated acid.

Unfortunately, $\dot{L}a$ has rarely been measured in exercising humans. Using the data of three studies (21, 22, 42), $\dot{L}a$ was analyzed with regard

to exercise intensity (Figure 4). The data are variable but regression analysis demonstrated a significant exponential relationship ($y = -0.54e^{0.03x}$; $r = 0.87$).

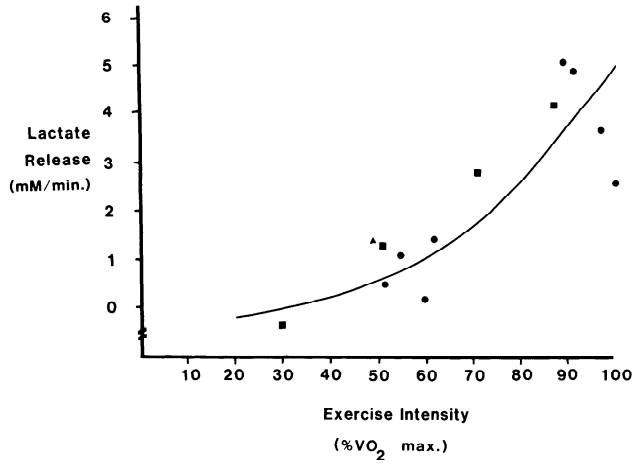


Figure 4. The lactate release response to increasing exercise intensity. The data are taken from three studies (21, 22, 42) and are represented by a triangle (22), squares (21) and circles (42).

It is tempting to conclude that the exponential increase in muscle lactate (Figure 3) (presumably resulting from a large positive modulation of glycolytic enzymes, and hence increased rate of supply of NADH and pyruvate for LDH) results in a rapid acceleration in lactate transport mechanism(s) and hence a similar exponential rise in blood lactate (Figure 1) (as release overwhelms blood lactate clearance). However, the relationship may not be so direct. Tesch et al. (40) and Jacobs and Kaiser (17) both report that at a blood lactate concentration of 4mM (i.e. somewhat above Owles' point and approximating the saturation point for La reported by Jorfeldt et al. (21)) muscle lactate can vary between subjects from 2.1 to 14.4 mM/kg. Similarly, Lollgen et al. (31) found that the muscle/blood lactate ratio can vary from 1.5 to 4.7 between subjects at 70% $\dot{V}O_2$max. Thus the muscle lactate - lactate release - blood lactate relationship is not as direct as the regression analysis might suggest.

Various studies have suggested that factors similar to those influencing lactate production rates (i.e. fiber type, capillary density, enzyme profile, etc.) are components in the regulation of lactate release. Although several studies have failed to demonstrate tissue hypoxia in active muscle which is releasing large quantities of lactate (8, 18), the concept that the initial increase in blood lactate is an 'anaerobic' threshold remains dominant in the literaure. Two of the three studies employed in Figure 3 provide data that clearly demonstrate that La and arterial lactate can be lowered 50-70% and 35-40% respectively while the $\dot{V}O_2$ of the exercising leg remains unchanged at work intensities and blood lactate levels that approximate Owles' point. Juhlin-Dannfelt and Astrom (22) reported these results upon administration of propranolol, while Welch et al. (42) had similar findings when subjects breathed hyperoxic gas (60% O_2) at 50-62% $\dot{V}O_2$max.

Summary

Owles' point and the accumulation of blood lactate encompass the processes of intramuscular lactate production, lactate release and lactate clearance. While blood and muscle concentrations and even La have changes that approximate exponential relationships that accelerate at work intensities of 50-70% $\dot{V}O_2$max, the underlying etiologies are very complex. Oxygen availability does not appear to be a factor in these processes at this range of work intensities. A more detailed understanding of the processes of lactate production, lactate oxidation and membrane transport (lactate release) are necessary before we will have a complete understanding of why blood lactate accumulates at this intensity of energy expenditure and what association it may have with the other components of anaerobic threshold.

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Methodologies for Measurement of the Anaerobic Threshold

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Introduction

In an incremental exercise test to exhaustion, the ventilation first increases linearly with respect to oxygen uptake ($\dot{V}O_2$), then increases more rapidly. The point at which this rapid increase in ventilation occurs has become known as the anaerobic threshold (21), or ventilatory anaerobic threshold (6). More recently, Jones and Ehrsam (13) have chosen the terminology, ventilatory threshold, to describe this same point to avoid any semantic discussion concerning cause and effect. This paper will continue to employ the descriptor "ventilatory threshold" for the same reason.

The purpose of this paper is to examine the methodology used to select the ventilatory threshold from exercise tests. To do this, it is first necessary to identify the basic mechanisms which might be responsible for the nonlinear behavior of the ventilatory response to exercise. The second and third topics addressed are the techniques and the type of exercise test used to measure the ventilation and gas exchange with special attention paid to how each of these might influence the selection of a ventilatory threshold. The fourth topic considers the various subjective criteria which are applied by different investigators to the selection of the ventilatory threshold. Finally, some comments will be made on the attempts in our laboratory to apply objective criteria with computer fitting of the exercise data.

The Venilatory Response to Exercise

The ventilatory threshold is associated with the onset of an excessive increase in the production of CO_2. Several mechanisms exist which could account for this increased $\dot{V}CO_2$. The concept of Wasserman et al. (21) was that increased H^+ associated with a sudden increase in lactate production (due to cellular hypoxia) was the cause of the increased $\dot{V}CO_2$ as the H^+ was buffered by HCO_3^- in the blood. The blood lactate concentration does increase around the point of the ventilatory threshold. However, intramuscular lactate begins to increase before the ventilatory threshold (6). This is reflected in the blood where lactate is also significantly elevated before the detection of a ventilatory threshold (6). Furthermore, some investigators have questioned whether a threshold for plasma lactate exists, or whether the response is a continuum with an exponential increase originating as soon as exercise begins (24). It has also been demonstrated by several investigators that the ventilatory and lactate thresholds can be dissociated by changes in the rate of increase in power output (9), by changes in pedaling frequency (8) and by manipulation of metabolic substrate (7, 15). Based on these lines of evidence, it is necessary to examine other potential mechanisms which might be implicated in the increase in the $\dot{V}CO_2$ at the point of the ventilatory threshold.

The metabolic respiratory quotient (RQ) increases progressively with increasing exercise intensity. Thus, with respect to the relationship between $\dot{V}_E$ and $\dot{V}O_2$, this ratio will increase as the ratio $\dot{V}_E/\dot{V}CO_2$ remains constant. This is a relatively small factor which will tend to bias the estimation of the ventilatory threshold.

CO_2 is stored in muscle and venous blood during exercise (14). However, the rate at which CO_2 is stored decreases with increasing levels of power output (10, 14). It has recently been shown that CO_2 can be excreted rather than stored when an increase in power output is associated with a metabolic acidosis (10). Near the ventilatory threshold, this could account for some of the increased CO_2 production.

The $\dot{V}_E$ is the sum of alveolar and dead space ventilation ($\dot{V}_E = \dot{V}_A + \dot{V}_D$). The ratio of dead space to tidal volume (V_D/V_T) decreases from rest to moderate levels of exercise, with the V_T reaching a plateau near the point of the ventilatory threshold (4). Above this point, $\dot{V}_E$ increases by an increase in breathing frequency. This change in ventilatory pattern will result in an increase in $\dot{V}_E/\dot{V}O_2$ (13).

That the relationship between $\dot{V}_E$ and $\dot{V}O_2$ should exhibit a threshold for disproportionate increase in $\dot{V}_E$ as factors responsible for the production of CO_2 change with exercise is well supported on theoretical and experimental grounds. While in some cases the relationship between this ventilatory threshold and the lactate threshold can be manipulated, it is clear from clinical experience that the ventilatory threshold has sound merit as a part of a complete assessment of aerobic fitness (12, 20) since this point correlates will with a marked increase in the sensation of effort. This idea is opposed by Yeh et al. (24) who concluded that it was invalid to determine a noninvasive ventilatory threshold if it could not be validated against an invasive threshold. Clearly, the two "thresholds" can be quite different in origin.

Measurement of Ventilation and Gas Exchange

Until recently, the use of open circuit gas collection and analysis techniques has been typical in exercise physiology laboratories and clinics. The data obtained from this type of measurement have been over fixed collection intervals which are occasionally as short as 15 s, but more typically are 30 to 60 s. Caiozzo et al. (2) have attempted to assess various noninvasive techniques for the evaluation of the ventilatory threshold with 30 s interval gas collections. In their Figure 3, they show 22 data points beyond the onset of the incremental exercise test. In this particular data set, this becomes a problem because of a very unusual rise in $\dot{V}CO_2$ at the point denoted the anaerobic threshold. This increase in $\dot{V}CO_2$ actually resulted in an atypical decrease in the $\dot{V}_E/\dot{V}CO_2$ ratio at that point. We previously published data from an incremental exercise test with 48 data points from an open-circuit system in the validation of a computer algorithm to detect the ventilatory threshold (see Figure 3 in reference 18). Since that time, we have used a breath-by-breath system which provides greater resolution of the course of the ventilatory and $\dot{V}O_2$ responses to exercise. In Figure 1 are the data from one subject from both a breath-by-breath (upper panel) and an open-circuit (lower panel) system. It is clear that the pattern of response in the breath-by-breath data is a smooth curve. In the open-circuit data, distinct line segments can be visualized.

The response of the $\dot{V}_E/\dot{V}O_2$ ratio is shown in Figure 2 for both data sets for this subject superimposed. While one could argue for the existence of a definite break point in the open-circuit data set at the point of the ventilatory threshold, the breath-by-breath data set shows no such clear break. Rather, the relationship gradually curves upward from its lower asymptote. Similar patterns are evident in Figures 3 - 5 of this paper. This raises a major problem with the selection of a ventilatory threshold; that is, what is the confidence limit over which the selection of a ventilatory threshold spans? It is typical for researchers to define one number as the threshold value. This problem will be discussed later in this paper as other aspects of definition of the ventilatory threshold are covered.

The Exercise Test Modality

The most commonly used exercise test modality has been the cycle ergometer. The advantage of being able to select the power output for the subject with some precision has made this the choice for research studies. The duration of the excercise test has recently been extensively considered. Whipp et al. (21) observed no significant difference in the parameters $\dot{V}O_2$max, ventilatory threshold, or work efficiency for cycle ergometer tests which were conducted as the typical step increment of work rate or as ramp increases in work rate with the ramp slope being in the range of 20-50 watts/min. These data have been confirmed for healthy subjects (9). However, for subjects of lower fitness, the rate of increase in work rate should be adjusted to bring the subject to exhaustion in about 10 minutes (1). This type of exercise test obtains the highest values for $\dot{V}O_2$max, but exercise duration has little effect on ventilatory threshold.

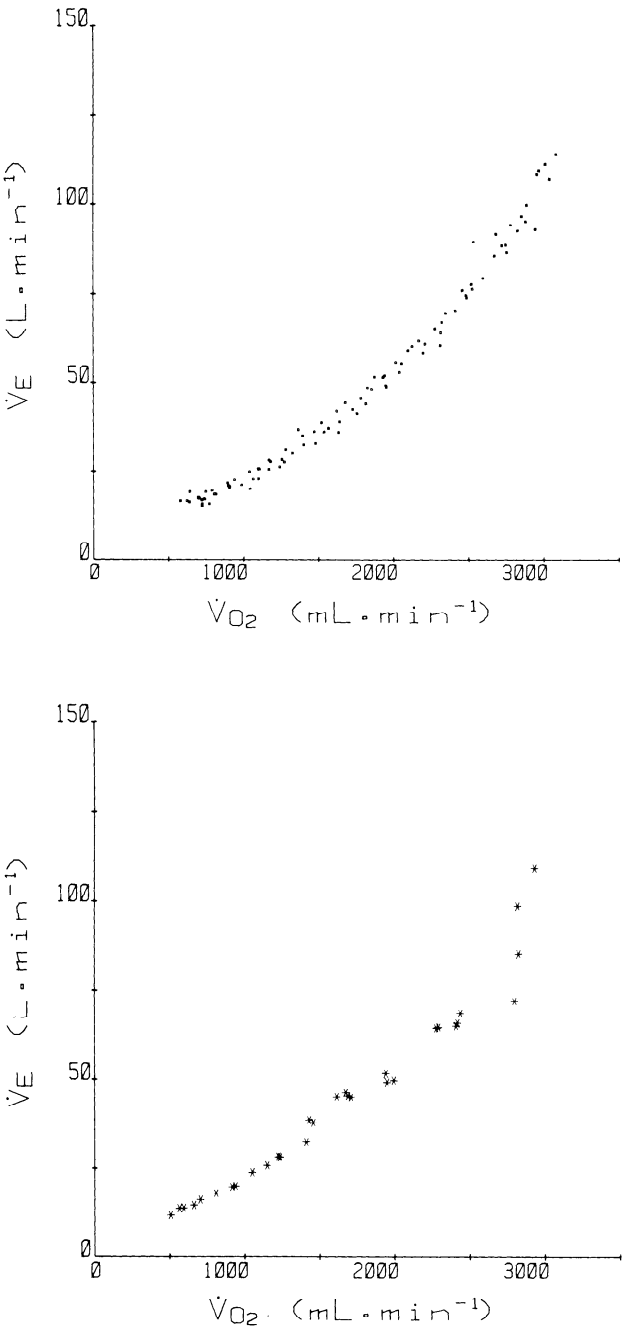

Figure 1. Upper panel: the breath-by-breath data for one subject during a 15 watts/min incremental exercise test for the variables, $\dot{V}_E$ and $\dot{V}O_2$. Lower panel: For the same subject as in the upper panel, data obtained on an open-circuit basis are displayed. This second 15 watts/min test was conducted on a different day than the test shown in the upper panel.

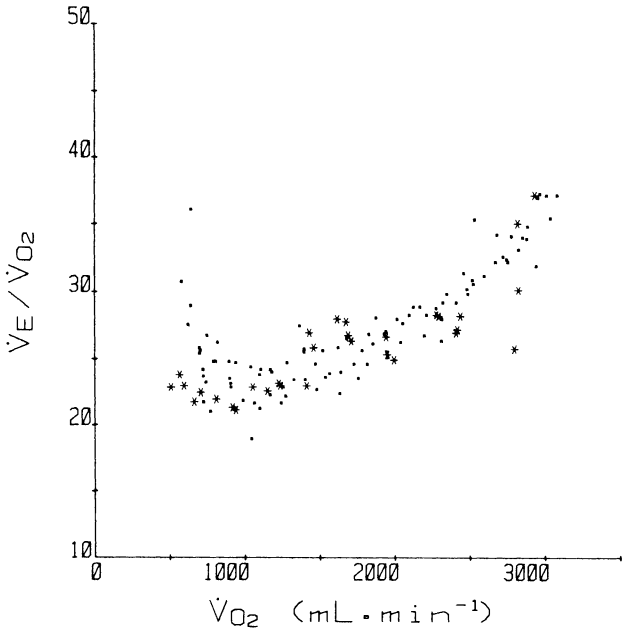

Figure 2. The $\dot{V}_E/\dot{V}O_2$ ratio is plotted against $\dot{V}O_2$ for the tests shown in Figure 1. Symbols are the same as Figure 1.

The precision with which the ventilatory threshold can be discerned has been claimed to be increased by using fast ramp increases in work rate (23). Hoever, more recent work from the same laboratory claims that the best discrimination is obtained with a slower rate of increase in work (1). In Figures 3, 4 and 5 are data obtained for one subject in three different ramp work tests in which the work rate increased at 8, 15, or 50 watts/min. These data show that the ventilatory threshold as determined by either the nonlinear increase in $\dot{V}_E$, the rapid rise of the $\dot{V}_E/\dot{V}O_2$ ratio, or the increase in end-tidal PO_2 are all subject to some slurring of the response over a range of $\dot{V}O_2$ values. The estimates for "threshold" points selected by three observers from coded plots of each variable are shown in Table 2. In each test, the ventilatory threshold cannot be precisely defined by a sharp break point. These data are typical of those obtained in a study of 8 normal subjects at each of these ramp work tests.

Determination of ventilatory threshold with treadmill testing has not been as widely reported as cycle testing. Davis et al. (3) reported that the treadmill ventilatory threshold occurred at the same percent of $\dot{V}O_2$max as that for cycle exercise. These results have been confirmed by Buchfuhrer et al. (1983). In conducting treadmill tests to determine the ventilatory threshold, care must be taken to obtain an adequate number of data points below the threshold to define the point of ventilation increase. Tests of normal subjects at 3.4 mph with grade increments of 1.7%/min proved to be adequate for defining the ventilatory threshold (1). However, tests of subjects running on the treadmill frequently give abnormally high estimates of ventilatory threshold as a % $\dot{V}O_2$max (19) since the initial work rates are equivalent to about 50% $\dot{V}O_2$max. These results have not been investigated by confirming the ventilatory thresholds of the same subjects in other standard exercise protocols.

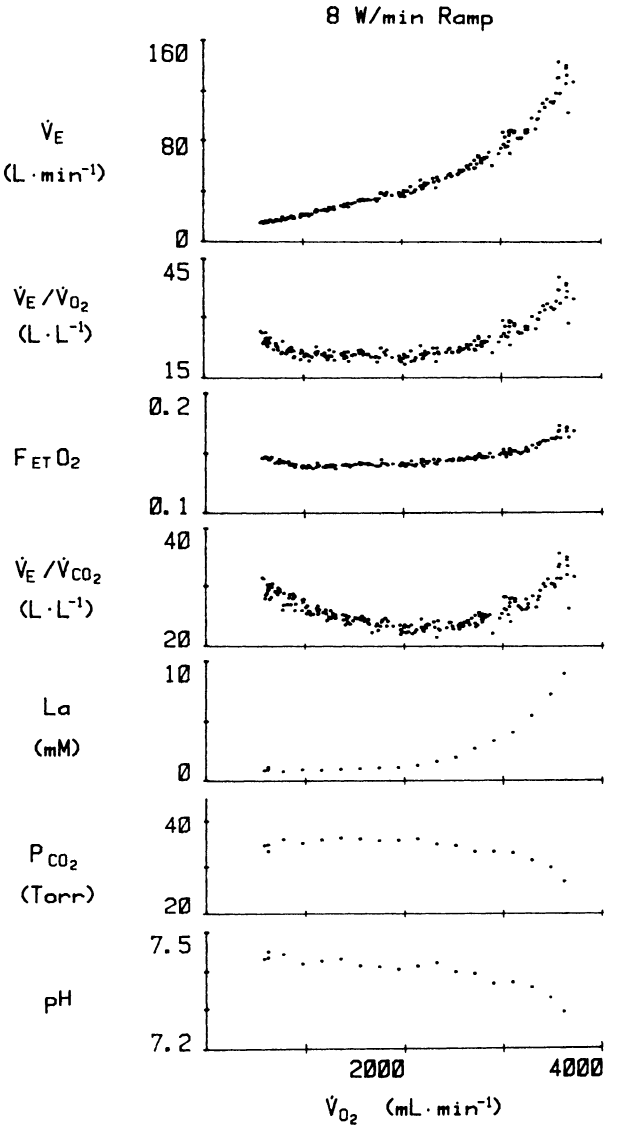

Figure 3. The breath-by-breath data of a single subject during an 8 watts/min ramp test have been averaged over 10 s intervals and plotted against $\dot{V}O_2$ for each of $\dot{V}_E$, $\dot{V}_E/\dot{V}O_2$. Also shown are arterialized venous blood values of lactate, PCO_2 and pH.

Arm cranking tests are typically associated with lower levels of both $\dot{V}O_2$max and ventilatory threshold (3). This could be a reflection of the lower levels of fitness in arms than in legs of average subjects.

Assessment Criteria for Ventilatory Threshold

The history of the study of the ventilatory threshold has recently been reviewed by Jones and Ehrsam (13). From the observation of Wells et al. (22) of a change in respiratory exchange ratio (R) associated with a metabolic acidosis, the work of Issekutz et al. (11) and Naimark et al. (17) expanded to note a ventilatory threshold which could be detected by a marked rise in the respiratory exchange ratio (R). Later, Wasserman et al. (21) used the disproportionate increase in $\dot{V}_E$ to demark the "anaerobic threshold". Since that time, many dif-

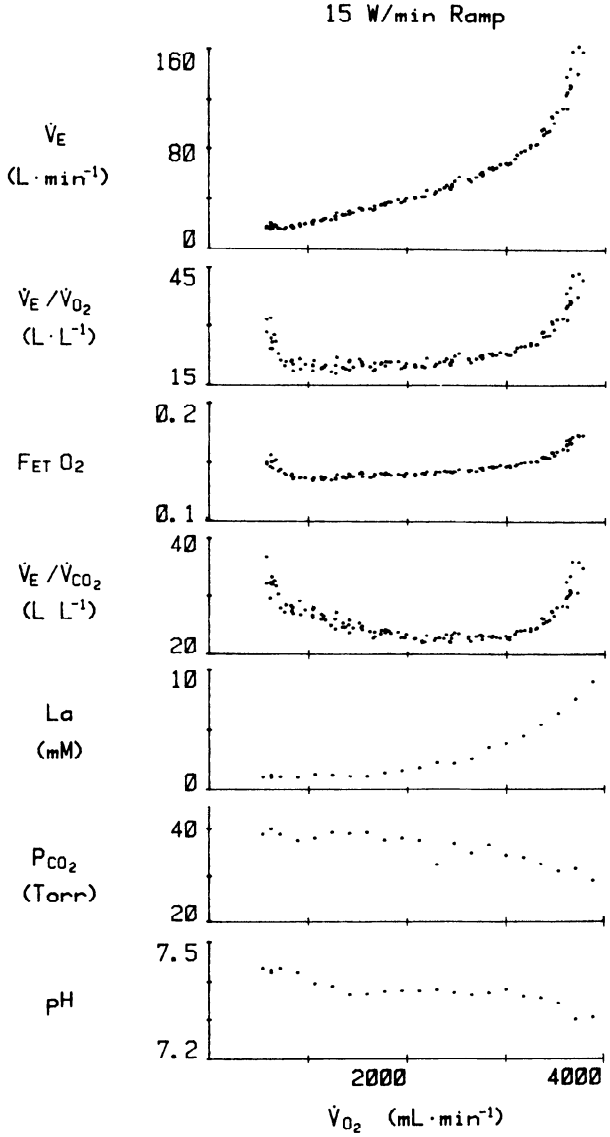

Figure 4. The data from a 15 watts/min ramp test for the same subject as in Figure 3 are shown.

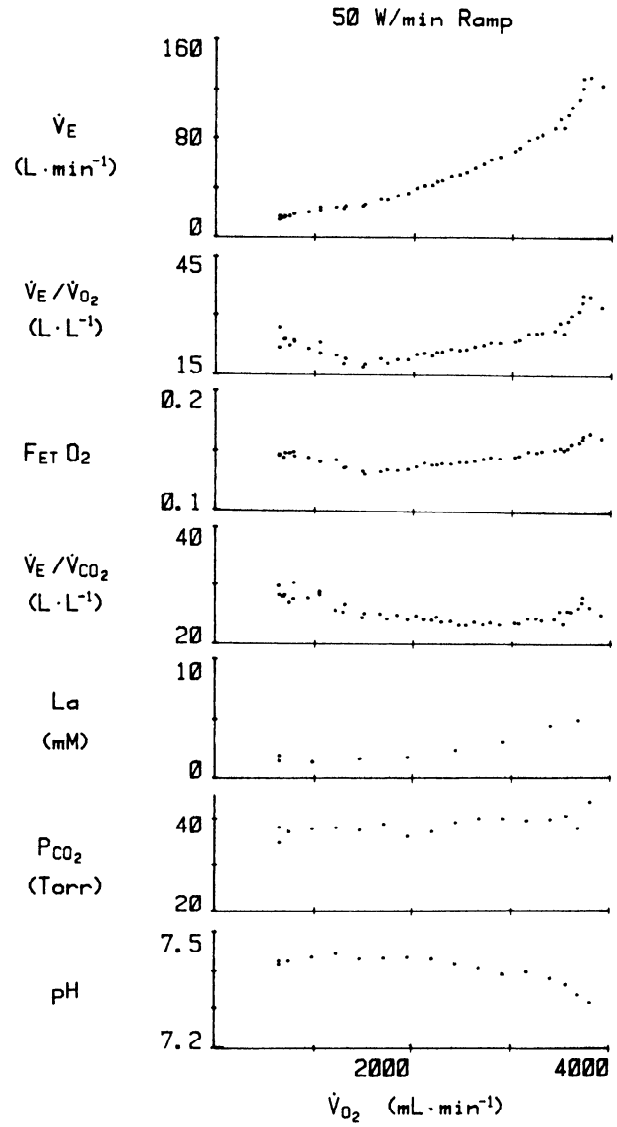

Figure 5. The data from a 50 watts/min ramp test for the same subject as in Figures 3 and 4 are shown.

ferent ventilatory variables have been used to define the point of the ventilatory threshold. Most recently, the group of Wasserman, Whipp and Davis has recommended the use of an increase in the ventilatory equivalent for oxygen uptake ($\dot{V}_E/\dot{V}O_2$) as the most sensitive indicator of the ventilatory threshold (20). This increase in $\dot{V}_E/\dot{V}O_2$ must occur in the absence of a change in the $\dot{V}_E/\dot{V}CO_2$ ratio to indicate that hyperventilation has not caused the change. In addition, the end-tidal PO_2 has been shown to decrease at the same point at which the $\dot{V}_E/\dot{V}O_2$ increases.

In a recent study of 8 healthy male subjects in our laboratory (Hughson, Green, Ursino, Inman and Bennett, unpublished 1984), we observed the responses to 8, 15 and 50 watts/min ramp increases in work rate. The subjects ($\dot{V}O_2$max = 3.70 $\pm$ 0.35 L/min) each performed two repetitions of the ramp tests. The data from the two tests were pooled for analysis. Blood was sampled from a vein in the back of a warmed hand for collection of arterialized blood. Ventilation and gas exchange were measured breath-by-breath with data averaged over 10 s intervals. All data were plotted on coded graphs. Each of three investigators, who were familiar with the published criteria for selection of the ventilatory threshold, had a set of coded graphs. The graphs were randomly mixed so that one subject's tests over the three work rates would not necessarily occur in sequence.

There were no significant differences in the $\dot{V}O_2$max of the subjects with the three different ramp work protocols (Table 1). Neither were there any differences in the $\dot{V}O_2$ at the ventilatory threshold determined from a mean of the individual observers' selections for the three variables: the point of nonlinear increase in $\dot{V}_E$ with respect to $\dot{V}O_2$, the increase in the $\dot{V}_E/\dot{V}O_2$ ratio, and the increase in the end-tidal fraction of O_2 ($FETO_2$, Table 1). However, the individual differences in selection of the point of ventilatory threshold is of major concern. In Table 2, the threshold values for each of the three observers are displayed. In all cases, it is possible to justify the selected points in spite of a range of differences of 25 to 1825 mL/min in $\dot{V}O_2$. These findings are similar to those

of Yeh et al. (24). Further, we have shown previously that the test-retest reliability of an individual observer is relatively low (r = 0.81 - 0.87) (18). Similar variability was noted by Gladden et al. (5) who sent nine experienced researchers in various laboratories data from 16 subjects in progressive exercise tests. The correlation coefficients relating different observers ranged from r = 0.37 - 0.96.

It has been reported that the $\dot{V}_E/\dot{V}O_2$ ratio provides the best test-retest correlation (r = 0.93) of any of the noninvasive measures of ventilatory threshold (2). That study used only a single investigator to evaluate the ventilatory threshold. In contrast, when three investigators reviewed plots independently, the range of selected values was very large for each of $\dot{V}_E$ versus $\dot{V}O_2$, $\dot{V}_E/\dot{V}O_2$ versus $\dot{V}O_2$, and $FETO_2$ versus $\dot{V}O_2$ as can be seen in Figures 3, 4 and 5 and Table 2.

It is clear from the data reported above and from the experience of other researchers that the subjective assessment of the ventilatory threshold is prone to variability. If it is necessary to use subjective means to determine the ventilatory threshold, it is highly recommended that the data be analyzed only from coded plots by several investigators. The mean value should be used to report the data. This is especially critical for research in which hypotheses exist concerning the potential alteration in the ventilatory threshold due to interventions such as training or administration of beta-blockers (e.g. 16).

Computer Determination of Ventilatory Threshold

The only published report of a computer algorithm for the selection of the ventilatory is that of Orr et al (12). This algorithm is based on the linear increase in $\dot{V}_E$ with respect to $\dot{V}O_2$ in exercise up to the ventilatory threshold. The model to fit the entire $\dot{V}_E$ versus $\dot{V}O_2$ response was three straight lines. As noted above, the data from open-circuit measurements of ventilation and gas exchange conformed to this model quite well. However, it was pointed out by Orr et al. (18) that the use of two straight lines above the ventilatory threshold was strictly a matter of fitting a curve better with two lines than with one. It is clear from breath-by-breath data that the response is truly curvilinear above the ventilatory threshold. The response has frequently been referred to as an exponential increase in $\dot{V}_E$. The physiological basis for such a response would be the increase in blood lactate above the so-called lactate threshold which has been shown to conform to an exponential increase (24). The consequence of applying the three segment linear model of Orr et al. (18) to data which are comprised of a linear segment followed by an exponential increase should be a tendency to slightly over-estimate the ventilatory threshold as the model tries to minimize the residual sum of squares. However, this was not true in all cases (Table 3).

There are disadvantages to the linear segment model. It is a pattern recognition program which cannot allow for major fluctuations in the subject's pattern of breathing. Examination of the $\dot{V}_E/\dot{V}O_2$ in conjunction with the $\dot{V}_E/\dot{V}CO_2$ might reveal hyperventilation as the cause of an assumed ventilatory threshold. However, subjects who hyperventilate frequently produce data which cannot be resolved by subjective assessment techniques either. While these problems are acknowledged, the computer is perfect in its ability to select the same point for the ventilatory threshold from a data set.

We have recently revised our computer model to select the ventilatory threshold. In the majority of cases examined, there are minor differences between the estimated values of the new and old models. The new routine confines the intercept of two adjacent segments to exist either at the data point which defines the break point in the data set, or in the interval between successive data in the set. Thus, for breath-by-breath data, the actual interval is very small. Statistically, it is a requirement of the determination that the intersection point for the segments must be a valid solution for the division of the data. With the three segment model, it is necessary that both intersection points satisfy this condition. This however, has not answered the problem of confidence limits for the ventilatory threshold. The reason for this is that the regression assumes that there is no error in the X-variable. However, $\dot{V}O_2$ values do have error in any measurememt system. The subjective estimates of ventilatory threshold shown above indicate the type of range which should be incorporated around a value assigned to the ventilatory threshold. Future research is needed into the problem of confidence limits for the ventilatory threshold.

The development of a model to fit the $\dot{V}_E$ versus $\dot{V}O_2$ data according to a linear segment followed by an exponential might provide a better estimate of the ventilatory threshold. We have used such a model; however, problems arise. The model is very demanding of computer time as exponential curve fitting is an iterative process requiring limits to be set for convergence criteria. Further, the same constraint defined above, that the intersection of the two lines must occur either at a data point or in the interval between two successive data points, must also be met. Finally, the nature of the exponential curve is such that the curve parameter can produce a line which approximates to a straight line in the region of the intersection of the linear and exponential segments. This might yield an artificially low value for the estimate of the ventilatory threshold.

Initially we chose the $\dot{V}_E$ versus $\dot{V}O_2$ relationship because it was possible to define an algorithm with an arbitrary intersection point. Just as the subjective evaluation of the ventilatory threshold has expanded to include other variables of ventilation and gas exchange, it might be necessary to develop a computer model which will evaluate the $\dot{V}_E/\dot{V}O_2$ ratio or some similar index as the ultimate objective criterion for selection of the ventilatory threshold.

Summary

The ventilatory threshold defines a parameter of the aerobic system which appears to be an important indicator of fitness in both patients and normals (12, 20). Further, the ventilatory threshold may prove to be a very sensitive indicator of interventions such as training. Clearly, the physiological basis for definition of a point in the ventilatory response exists. Thus, in contrast with Yeh et al, (24), it is concluded that the ventilatory threshold should be considered in fitness tests whether a blood lactate response has been shown to coincide with the

point or not. The method used to assess the ventilatory threshold requires additional research. It is important that we obtain a method to evaluate the confidence limit around an estimate due to normal physiological variability and due to measurement error; and it is important that we eliminate the error introduced by human variability in selection of the threshold point.

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Table 1*

Effect of Different Ramp Increases in Work Rate on Ventilatory Threshold (VT) and $\dot{V}O_2max$

	8 watts/min ramp	15 watts/min ramp	50 watts/min ramp
VT by $\dot{V}_E$ (mL O_2/min)	2307 ± 370	2314 ± 471	2199 ± 505
VT by $\dot{V}_E/\dot{V}O_2$ (mL O_2/min)	2453 ± 464	2425 ± 557	2300 ± 603
VT by $FETO_2$ (mL O_2/min)	2635 ± 435	2602 ± 454	2593 ± 662
$\dot{V}O_2max$ (mL/O_2min)	3655 ± 495	3732 ± 350	3729 ± 382

*Values are means ± S.D. for 8 subjects, 3 observers. See text for methods of selecting ventilatory threshold. In some cases, the observers elected not to indicate a threshold as the data were curvilinear.

Table 2

Values (in mL O_2/min) selected as "thresholds" for each of the variables from one subject shown in Figures 3, 4 and 5 by each of three investigators. Computer selected value for ventilatory threshold is shown for $\dot{V}_E$ versus $\dot{V}O_2$.

Exercise Test = 8 watts/min ramp.

Observer	$\dot{V}_E$	$\dot{V}_E/\dot{V}O_2$	$FETO_2$	La	pH
1	2150	2400	2900	2025	2550
2	2150	2450	2225	2075	2400
3	2175	2300	3100	1150	2500
Computer	2474				

Exercise Test = 15 watts/min ramp.

Observer	$\dot{V}_E$	$\dot{V}_E/\dot{V}O_2$	$FETO_2$	La	pH
1	2625	3100	3000	1700	3075
2	2375	2350	2800	1800	3125
3	2150	2200	2500	1675	3125
Computer	2239				

Exercise Test = 50 watts/min ramp.

Observer	$\dot{V}_E$	$\dot{V}_E/\dot{V}O_2$	$FETO_2$	La	pH
1	1500	1500	3525	2300	2175
2	2275	1950	3025	2050	2300
3	1650	1775	1700	1100	1900
Computer	1867				

Table 3

Ventilatory Threshold (in mLO_2/min) for 3 Subjects Determined by 3 Observers* and the Computer Model

	8 watts/min		15 watts/min		50 watts/min	
Subject	Observers	Comp	Observers	Comp	Observers	Comp
1	2150	2474	2375	2239	1700	1867
2	2350	2040	2500	2611	2300	2312
3	3070	3080	2460	2291	3080	1456

*Values given for observers are the means calculated from a combination of three indices ($\dot{V}_E$ versus $\dot{V}O_2$, $\dot{V}_E/\dot{V}O_2$ versus $\dot{V}O_2$ and $FETO_2$ versus $\dot{V}O_2$) for 3 observers.

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Current "Anaerobic Threshold" Controversies

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Introduction

The anaerobic threshold concept has generated controversy since its inception. This controversy has intensified since 1973 when Wasserman et al. (44) defined the anaerobic threshold as "the level of work or O_2 consumption just below that at which metabolic acidosis and the associated changes in gas exchange occur". Wasserman et al. (44) attributed this threshold to an inadequate O_2 delivery to the working muscles which in turn resulted in anaerobic metabolism and lactic acid formation. Since the threshold was usually observed at a work rate requiring only about 1/2 to 2/3 of the maximal O_2 uptake ($\dot{V}O_2max$), the role of hypoxia was questioned. Many investigators believe that factors other than muscle hypoxia, such as recruitment of fast twitch fibers, regulation of enzymatic activity and changes in the rate of lactate removal, are responsible for the increase in blood lactate and therefore have called the term, anaerobic threshold, a misnomer. Other investigators have questioned the ability to measure the anaerobic threshold accurately and reliably. Still others have questioned the idea that lactate efflux from muscle into blood goes hand-in-hand with hydrogen ion efflux in the same direction. This presentation is organized to reflect these controversies with topics of discussion in the following order: 1) Muscle hypoxia and lactate production, 2) Alternative factors which can increase blood lactate concentration, 3) Measurement of the anaerobic threshold, 4) Lactic acid and hydrogen ions, 5) Anaerobic threshold mechanisms: two views, and 6) Conclusions.

Muscle Hypoxia and Lactate Production

For almost one hundred years it has been known that hypoxia stimulates an increase in blood lactate concentration (Araki cited in (31)). In the early 1920's, Hill and his colleagues (17, 18) performed several studies on isolated muscles in vitro; these studies confirmed the role of hypoxia in lactic acid production. It was this early research which firmly established the idea that an increase in lactate concentration indicates an inadequate O_2 supply. Recently, Wasserman (42) has summarized the arguments which support the role of hypoxia in the increase in blood lactate during exercise. Hogan et al. (19) have published data, illustrated in Figure 1, which are typical of the effects of breathing even mildly hypoxic gas mixtures (FIO_2 = 0.17) on blood lactate concentration during an incremental work test. Figure 1 also shows the effect of breathing hyperoxic gas mixtures (FIO_2 = 0.60) on blood lactate concentration. These results appear to agree with the idea that hyperoxic gas mixtures allow a greater O_2 delivery to the exercising muscles, thus alleviating muscle hypoxia and reducing lactic acid production. However, Welch et al. (45) have shown that hyperoxia reduces muscle blood flow during leg exercise so that O_2 delivery (the product of blood flow and arterial O_2 content) during hyperoxic exercise is not significantly different from normoxic conditions. Therefore, the reduction in blood lactate concentration during hyperoxia must be due to something other than a simple mitigation of hypoxia in the exercising muscles.

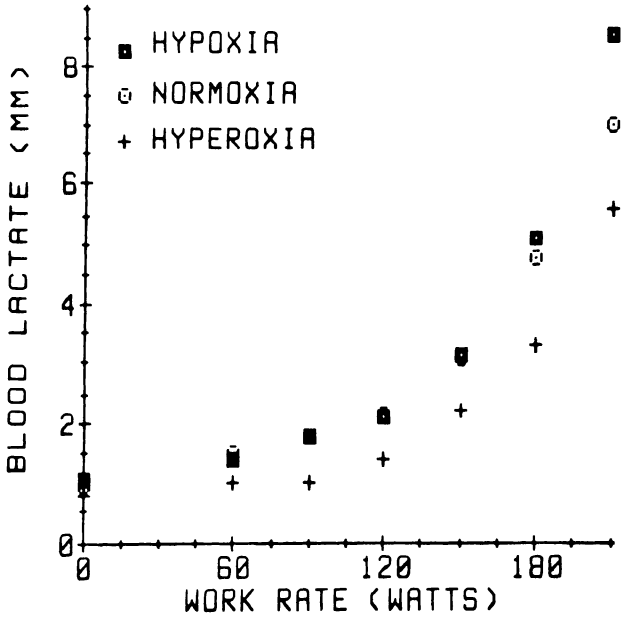

Figure 1. Effect of hypoxia (FIO_2 = 0.17), normoxia (FIO_2 = 0.21) and hyperoxia (FIO_2 = 0.60) on blood lactate concentration during incremental exercise. (Redrawn from Hogan et al. J. Appl. Physiol. 55:1134-1140, 1983.)

Physical training results in a decrease in blood lactate concentration at a given submaximal work rate and at the same relative work intensity (25). (See Figure 2.) For a long time it was believed that this reflected an increased O_2 delivery to the exercising muscles due to cardiovascular adaptations caused by training (21). However, this interpretation is weakened by the

fact that blood flow per kg of exercising muscle is actually lower in trained than in untrained subjects at the same absolute, submaximal work rate (14, 41). Evidence from studies in which substrate availability to exercising muscles was altered has also shown that factors other than O_2 delivery can change the blood lactate response to exercise. For example, both glycogen depletion (24) and high blood free fatty acid concentration (26) result in a lower blood lactate concentration for a given work rate during incremental exercise and an increase in the work rate at which the anaerobic threshold occurs.

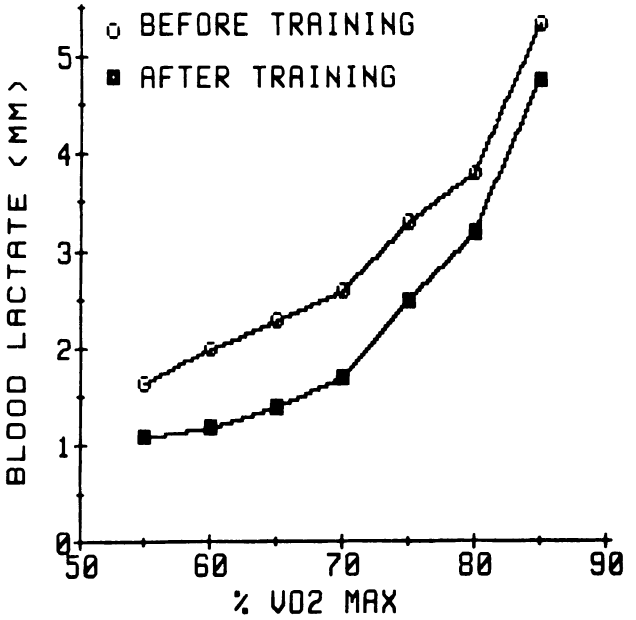

Figure 2. Blood lactate concentration at the same relative intensity (% of $\dot{V}O_2$max) before and after training. (Redrawn from Hurley et al. J. Appl. Physiol. 56:1260-1264, 1984.)

More direct evidence against hypoxia as the cause of lactic acid production during muscle contractions has come from the reflectance fluorometry study of Jöbsis and Stainsby (28). If hypoxia is severe enough to interfere with oxidative metabolism, a reduction of the members of the respiratory chain would be expected. To the contrary, Jöbsis and Stainsby (28) observed a decrease in NADH fluorescence, indicative of NADH oxidation, within five seconds after the beginning of twitch contractions in both gastrocnemius and gracilis muscles of the dog. The twitch rates that were used always resulted in a large lactate release from the muscles. Therefore, the combination of lactate release and NADH oxidation suggests that the lactic acid production was not due to hypoxia.

Horstman et al. (23) have criticized the investigation of Jöbsis and Stainsby (28), indicating that the comparison of NADH fluorescence during contractions with the resting fluorescence was inappropriate. They suggested that the correct comparison would be between contractions which did produce lactate and contractions which did not. NADH fluorescence at rest was very high in the study of Jöbsis and Stainsby (28), probably because of a low ADP concentration (23). For this reason, Honig (22) suggested that any increase in NADH fluorescense in hypoxic cells at the onset of contractions could have been obscured by a decreased fluorescence in a few other well-oxygenated cells. In addition, Wasserman (42) has questioned the relevance of the findings of Jöbsis and Stainsby (28) since their technique measured only mitochondrial NADH fluorescence, but could not detect cytoplasmic NADH. Despite these criticisms, Connett et al. (8) have recently confirmed the production of lactate in the absence of hypoxia in dog gracilis muscles using an entirely different technique. It is generally accepted that the critical PO_2 for $\dot{V}O_2$ of isolated mitochondria in state 3 is around 0.5 Torr (6). Connett et al. (8) combined myoglobin cryomicrospectroscopy with tissue sampling to obtain the PO_2 distribution in subcellular volumes and to estimate lactate concentration in the population of cells used for spectroscopy. Their results indicated that lactate accumulated in the muscles as metabolic rate increased, in spite of the fact that there were no loci with PO_2 less than 2 Torr through 70% of $\dot{V}O_2$ max. In other words, there were no O_2-limited mitochondria.

Alternative Factors Which Can Increase Blood Lactate Concentration

If the increase in blood lactate concentration during exercise is not due to hypoxia, what is the stimulus for the increase? Some investigators have suggested that blood lactate increases could be due to the recruitment of fast twitch muscle fibers (4). Indeed, Baldwin et al. (1) reported that in rats running on a treadmill, there was a large increase in lactate concentration in FG fibers of the hindlimb as exercise intensity was increased. At the same time there were relatively minor changes in lactate in SO and FOG muscle fibers. This supports the possibility that fast twitch fiber recruitment instead of muscle hypoxia may be responsible for increases in blood lactate during incremental exercise. In addition, analysis of lactate concentration in muscle biopsies from humans revealed that muscle lactate accumulation occurred well in advance of increases in blood lactate (13). Therefore, if there is an anaerobic threshold in contracting muscle, it precedes the threshold that is determined by blood lactate observations.

Holloszy and Coyle (21) have emphasized the role of enzymatic activity and regulatory mechanisms in determining lactic acid production. The major fates of pyruvate are oxidation by the tricarboxylic acid (TCA) cycle, conversion to lactate by lactic dehydrogenase and conversion to alanine by alanine transaminase. Lactate formation can occur even in the presence of O_2 if the overall rate of glycolysis is rapid and lactic dehydrogenase (LDH) competes favorably for pyruvate, ADP and NADH with the TCA cycle and the alanine transaminase reaction. The effects of training on enzyme activities suggest that these intramuscular changes are responsible for the lower blood lactate levels observed following training. For example, it appears that the same rate of muscle O_2 utilization can be achieved at a lower ADP (primary regulator of mitochondrial respiration) concentration following training due to a higher muscle mitochondrial content. The lower ADP level should coincide with lower levels of AMP, P_i, and ammonia, and higher levels of ATP; a combination which should result in a relative inhibition of phosphofructokinase and therefore a slower glycolytic rate (21). In addition, there is a decrease in total LDH activity, an increase

in the capacity of the malate-aspartate shuttle to move NADH from the cytoplasm to the mitochondria (21), and an increase in alanine transaminase activity (20) following training. All of these adaptations should decrease the ability of LDH to compete with the mitochondria for pyruvate and thus lead to lower blood lactate concentrations following training, regardless of any considerations of 0_2 availability (21).

Recently, Brooks and colleagues (4, 10, 40) have emphasized the fact that blood lactate concentration does not indicate lactic acid production, but instead reflects the relative rates of entry into and exit from the blood. Although lactic acid production increases as exercise increases, the failure of lactate removal to keep pace may be a key factor in the blood lactate increase. Using ^{14}C-lactate tracer studies, Donovan and Brooks (10) have reported that training does not change lactate production, but instead increases the lactate clearance rate. Maintenance of the same lactate production following training in the face of the well-known decrease in RQ (indicative of less carbohydrate utilization and a lower glycolytic flux) is puzzling. This finding is in sharp contrast to what would be expected on the basis of the enzymatic adaptations to training (21), and promises to be a future area of controversy.

Summarizing to this point, the primary controversy surrounding the anaerobic threshold concept has been and continues to be whether or not the threshold is due to inadequate 0_2 delivery and consequent muscle hypoxia. In other words, is the anaerobic threshold really anaerobic? Almost one hundred years of evidence has clearly demonstrated that hypoxia does indeed result in lactic acid formation. Equally strong evidence has clearly demonstrated that lactic acid formation can and does occur in the absence of hypoxia. The balance of recent evidence favors factors other than hypoxia as the cause of an increase in blood lactate concentration during exercise. However, an incontrovertible resolution of this debate must await the development of techniques which will allow the measurement of PO_2 in small volumes of muscle tissue in exercising humans at the anaerobic threshold.

Measurement of the Anaerobic Threshold

A second important controversy has concerned the question of whether or not there is a close correspondence between the anaerobic threshold determined noninvasively from gas exchange variables (AT_{GE}) and the anaerobic threshold determined from an abrupt increase in blood lactate concentration (AT_{LA}). An associated debate concerns the reliability of the AT_{GE} determination. The gas exchange alterations attributed to the onset of metabolic acidosis during incremental exercise by Wasserman et al. (44) include: 1) a nonlinear increase in minute ventilation ($\dot{V}_E$), 2) a nonlinear increase in CO_2 output ($\dot{V}CO_2$), 3) an increase in end-tidal PO_2 without a corresponding decrease in end-tidal PCO_2 and 4) an increase in the gas exchange ratio (R). As noted above, the metabolic acidosis was in turn attributed to an abrupt increase in lactic acid production due to muscle hypoxia.

Beginning with the study of Davis et al. (9), several studies (5, 27, 34, 35, 47) have reported that there is indeed no significant difference between AT_{GE} and AT_{LA}. Correlation coefficients between AT_{GE} and AT_{LA} in these studies ranged from 0.87 to 0.95 with regression equations between the two variables lying very close to the line of identity. Slopes of the regression lines (AT values in l/min of $\dot{V}O_2$) ranged from 0.91 to 1.03 and the intercepts ranged from 0.07 to 0.83. However, other recent studies (13, 15, 24, 38, 46) have questioned a direct association between AT_{GE} and AT_{LA}. Hagberg et al. (15) demonstrated an AT_{GE} in subjects who were McArdle's syndrome patients. This is a significant finding since these patients lack the enzyme, phosphorylase, and are therefore unable to catabolize glycogen and form lactic acid. Figure 3 illustrates the ventilatory threshold in the absence of an increase in blood lactate concentration during incremental exercise in these patients.

In a study of normal subjects, Simon et al. (38) reported that in four of their five subjects, the AT_{GE} occurred at a lower work rate than the AT_{LA}. In contrast, Green et al. (13) used a computer program to determine the AT_{GE} and AT_{LA}, and reported that the AT_{GE} occurred at a significantly higher work rate than AT_{LA}. Yeh et al. (46) compared the AT_{LA} determinations of four experienced exercise physiologists on identical data. In their study, a ramp test (1.0 watt per 3.0 sec) was used and arterial blood samples were collected for lactate analysis. They found poor agreement among the evaluators with the range of AT_{LA} values in a typical test being greater than two min. In addition, there was at least a 10% uncertainty among the evaluators in the AT_{GE} measurement. Yeh et al. (46) concluded that: 1) the anaerobic threshold is not detectable with invasive methods (either arterial or venous blood lactate concentration), and 2) the AT_{GE} determination has too large a range of reviewer variability to be suitable for clinical use.

Recent results from my laboratory (12 and unpublished results) at least partly support the conclusions of Yeh et al. (46). In our study, nine evaluators from different laboratories determined the AT_{GE} and AT_{LA} from plots which were coded so that the evaluators did not know which lactate plots corresponded with the gas exchange plots. The gas exchange variables were calculated at 15 sec intervals using a mixing chamber technique. The results of this study indicated that 1) AT_{GE} measurements do not accurately predict AT_{LA} and 2) the AT_{GE} measurements are not reliable. Figure 4 illustrates the first conclusion. This figure shows the plot of AT_{GE} versus AT_{LA} for the two most experienced evaluators in the study. Note that although one of the evaluators had a relationship that was near the line of identity, the other did not. For all nine evaluators, the slope of the relationship between AT_{GE} and AT_{LA} ranged from 0.191 to 0.808 when the AT values were expressed in units of liters/min of 0_2 uptake. A perfect correspondence between the two measures would have yielded slopes near 1.0. Correlations among the AT_{GE} values for the different evaluators ranged from 0.30 to 0.93 with a median correlation of only 0.74. Even when the correlations between AT_{GE} values were high, the slopes relating the values were usually far from the line of identity.

We found better agreement between the AT_{LA} determinations of the different evaluators. Correlations for AT_{LA} values ranged rom 0.75 to 0.99 with a median correlation of 0.87. In addition, equations relating the AT_{LA} choices among the

different evaluators were closer to the line of identity than were those for AT_{GE} choices. This better agreement for AT_{LA} determinations occurred despite the fact that the blood lactate responses were clearly curvilinear, and therefore without any abrupt increase in blood lactate concentration. Figure 5 shows a typical example of the changes in blood lactate concentration with time in an incremental exercise test.

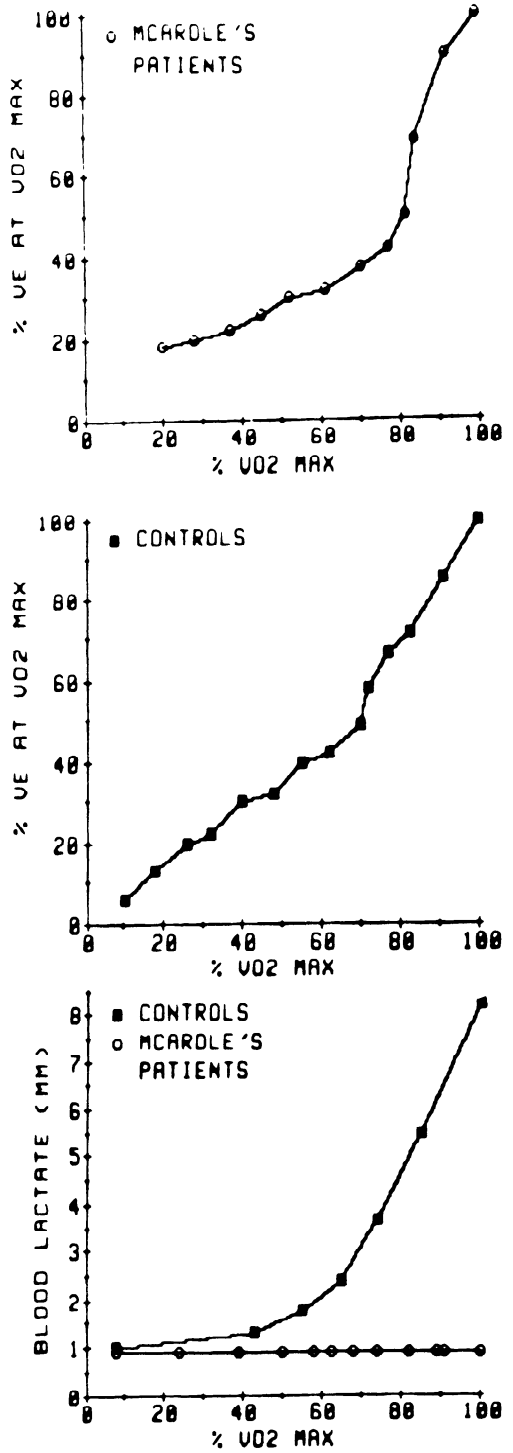

Figure 3. Ventilation and blood lactate response to incremental exercise in normal subjects (controls) and subjects with McArdle's Syndrome. Note the rapid increase in ventilation at about 50% of $\dot{V}O_2$max in the patients, despite the fact that there was no change in blood lactate concentration. (Redrawn from Hagberg et al. J. Appl. Physiol. 52:991-994, 1982.)

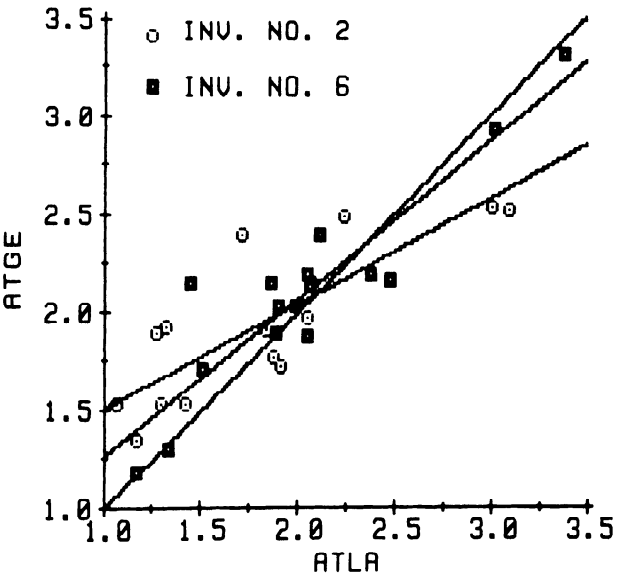

Figure 4. Comparison of AT_{GE} and AT_{LA} selections for two experienced evaluators. Although the regression line for Investigator No. 6 is close to the line of identity, this is not the case for Investigator No. 2. See text for details. (Unpublished results of Gladden, Yates, Stremel and Stamford.)

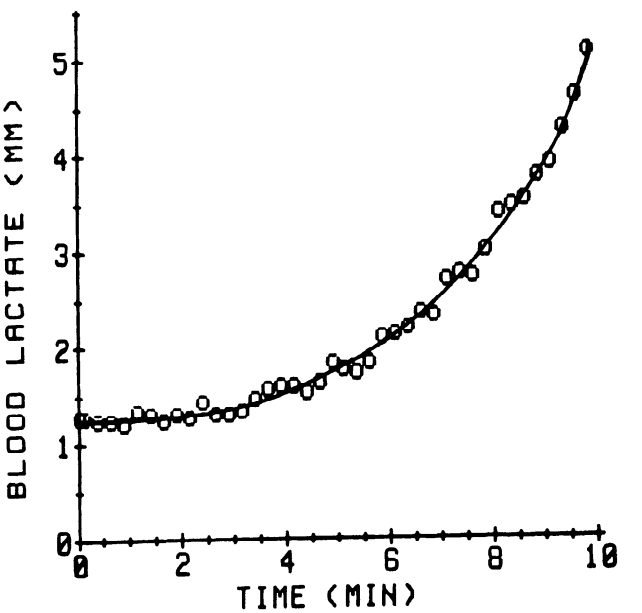

Figure 5. Typical blood lactate response to incremental exercise. Arterialized venous blood samples were taken every 15 seconds as work rate was increased by 30 watts each minute. (Unpublished results of Gladden, Yates, Stremel and Stamford.)

Taken as a whole, the evidence questions the reliability of the AT_{GE} determination and the ability to noninvasively determine the anaerobic threshold. These reservations apply especially to the routine clinical use of the anaerobic threshold and the determination of the anaerobic threshold by inexperienced investigators. However, we cannot rule out the possibility that a combination of experience and the use of sophisticated breath by breath gas exchange measurements negates these reservations. In addition, further refinement of the criteria for threshold determinations along with the use of computer programs raises the possibility of improving the quality of these measurements (13).

It is on the basis of the two controversies discussed above that a large number of terms have been used in place of "anaerobic threshold". Included among these replacement terms are Owles' point (30), the onset of plasma lactate accumulation (OPLA) (11), the onset of blood lactate accumulation (OBLA) (32), the lactate threshold (T_{lact}) (24), the lactate turn point (37), the maximal steady state(33), the lactate and ventilation inflection points (4), the ventilatory threshold (T_{vent}) (24), the proportional limit (30) and AT_{GE} and AT_{LA} (47) as used above.

Lactic Acid and Hydrogen Ions

A third controversy involving the anaerobic threshold has surfaced recently. The association of gas exchange alterations with lactic acid production at the anaerobic threshold is predicated on the idea that hydrogen ions from lactic acid are buffered mainly by bicarbonate in the blood thus forming CO_2 in addition to that which is metabolically produced. This additional CO_2 is given off in the lungs, resulting in an increase in $\dot{V}CO_2$ and R (44). As a result of the increase in $\dot{V}CO_2$ and perhaps the hydrogen ion, an increase in $\dot{V}_E$ occurs. It has been shown that the decrease in plasma bicarbonate concentration which occurs during exercise is approximately equal to the increase in plasma lactate concentration (43). This supports the notion that the lactate anion and the hydrogen ion leave the muscle together or at least leave at the same time and in equal amounts; and that the noninvasive gas exchange measurements are an indication of lactic acid production.

However, several recent studies have reported that hydrogen ion efflux from contracting muscle greatly exceeds the lactate output (2, 3, 7), and that the kinetics of hydrogen ion and lactate efflux are different (3). During continuing repetitive maximal twitch contractions in the in situ dog gastrocnemius muscle, non-CO_2 acid output was almost five times greater than the concomitant lactate output (2). During progressive working contractions in the same muscle, acid output was up to 11 times greater than lactate output (7). Benade and Heisler (3) stimulated isolated rat diaphragms and frog sartorius muscles to accumulate lactic acid. Subsequently, the rate of hydrogen ion efflux exceeded that of lactate ions by factors of 14 and 50 in the case of diaphragm and sartorius muscles respectively. Data of this type led Jones (20) to the obvious conclusion that the efflux of hydrogen ions and lactate ions from lactic acid formation may not go strictly hand-in-hand, and that changes in blood lactate concentration may not be quantitatively related to the flow of hydrogen ions from contracting muscle. The implication is that even if AT_{GE} can be measured reliably, it may be more closely associated with blood hydrogen ion concentration and/or bicarbonate concentration than with blood lactate concentration.

Anaerobic Threshold Mechanisms: Two Views

On the basis of information currently available, at least two schemes of the "anaerobic threshold" concept can be outlined. The traditional view, as first described by Wasserman et al. (44) and recently summarized by Wasserman (42), holds that the local O_2 supply in working muscle becomes inadequate at a submaximal work rate, typically in the range of 50 to 70% of the $\dot{V}O_2$max. As a result, the rate of ATP generation from aerobic mechanisms is insufficient, and anaerobic glycolysis is increased to supply ATP at the required rate. Lactic acid production is increased by the increase in anaerobic glycolysis, and an abrupt increase in blood lactate concentration ensues. The lactic acid is buffered predominantly by the bicarbonate system, both in the muscle where it is formed and in the blood. Buffering by bicarbonate leads in turn to the formation of additional CO_2, referred to as non-metabolic CO_2. The additional CO_2 is exhaled in the lungs, resulting in an increase in $\dot{V}CO_2$ and R. Ventilation ($\dot{V}_E$) also increases nonlinearly at this point due to the stimulation of the increase in $\dot{V}CO_2$ and perhaps due to a slight increase in hydrogen ion concentration. The increase in $\dot{V}_E$ is relatively greater than the corresponding increase in $\dot{V}O_2$ at this point during incremental exercise, thus leading to an increase in end-tidal PO_2 and an increase in the ventilatory equivalent for O_2, $\dot{V}_E/\dot{V}O_2$. Since both $\dot{V}_E$ and $\dot{V}CO_2$ increase at the same time, there is no change in either end-tidal PCO_2 or the ventilatory equivalent for CO_2 ($\dot{V}_E/\dot{V}CO_2$) at the anaerobic threshold.

An alternative scheme, based on recent evidence, is that lactic acid production increases with even very light exercise. However, lactic acid removal initially keeps pace with the increased production and there is no discernible increase in blood lactate concentration. As the work rate increases, lactic acid production outstrips lactic acid removal, leading to an increase in blood lactate level (40). In this scheme, the increase in lactic acid production is not due to hypoxia, but is instead the result of an increase in glycolytic rate and the balance of competition for pyruvate, ADP and NADH between LDH on the one hand, and alanine transaminase and the TCA cycle on the other. As work rate increases, the glycolytic rate is enhanced by the continued activation of phosphorylase and phosphofructokinase. Phosphorylase is activated directly by muscle contractions, perhaps by way of an increase in calcium concentration (36). In addition, sympathoadrenal activity increases as exercise intensity increases, resulting in an increase in the circulating levels of norepinephrine and epinephrine (16). These hormones, especially epinephrine, also activate glycolysis by way of phosphorylase activation (36). The increased sympathoadrenal activity also causes vasoconstriction and decreased blood flow to liver, kidney and inactive muscle. Decreased blood flow to these areas results in less lactate oxidation and less lactate removal from the blood (4). Increases in exercise intensity also decrease ATP concentration while increasing the concentrations of ADP, AMP, P_i and ammonia all of these changes tend to activate phosphofructokinase and increase lactic acid production (21). Increases in lactic acid production are hastened by the recruitment of fast twitch muscle fibers as exercise intensity increases; these fibers have an LDH isozyme pattern that favors lactic acid production (39). As lactic acid production increases relative to lactic acid removal, muscle lactate concentration builds up. The increase in muscle lactate is followed by increases in blood lactate concentrate as lactate leaves the working muscles and enters the blood. Since lactic acid production increases even with light exercise and gradually intensifies with increasing work rate, muscle and blood lactate concentration increase in a curvilinear (perhaps exponential) manner; there is no abrupt increase and therefore the choice of a threshold for either increased muscle or blood lactate represents an arbitrary decision. Figure 5 illustrates this point.

As muscle and blood lactic acid increase, there is an increase in hydrogen ion concentration, accompanied by buffering and an increase in CO_2 flux to the lungs. Hydrogen ions may be released

from sources other than lactic acid as well. Certainly, the changes in hydrogen ion concentration and $\dot{V}CO_2$ influence ventilation. However, this does not imply a cause and effect relationship between the curvilinear increases in blood lactate and ventilation which occur during incremental exercise. This idea is supported by Hagberg et al.'s (15) study of McArdle's syndrome patients. Although the ventilatory threshold may be worthy of study, it is not necessarily a direct consequence of lactic acid production or hypoxia. The ventilatory control system is a redundant system which has many regulating factors, some of which are humoral while others are neural.

Conclusions

In conclusion: 1) The primary controversy of whether or not the anaerobic threshold is due to hypoxia has not been finally resolved. Circumstantial evidence is abundant, but measurement of PO_2 in the micro-environment of the mitochondria at the anaerobic threshold in exercising humans is currently impossible. 2) A more recent debate concerns the ability to accurately and reliably measure the anaerobic threshold by noninvasive methods, and whether or not the gas exchange anaerobic threshold is a useful indicator of an abrupt increase in blood lactate concentration or the onset of lactic acid production. There is enough evidence to question the routine clinical use of the anaerobic threshold and the determination of the anaerobic threshold by inexperienced investigators. Whether or not experienced investigators using sophisticated techniques are able to accurately and reliably measure the anaerobic threshold is still a matter of discussion. In addition, further refinement of the criteria for threshold determinations along with the use of computer programs raises the possibility of improving the quality of these measurements. 3) Recent investigations have suggested that the scheme of non-metabolic CO_2 production due to the buffering of lactic acid by bicarbonate during exercise may be too simplistic. It appears that acid efflux from contracting muscle can exceed lactate efflux and may also have a different time course. 4) Finally, the increases in blood lactate concentration and ventilation during incremental exercise are not necessarily cause and effect, and they can be explained by factors other than hypoxia.

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